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A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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In Post-Tonsillectomy
GRANULAR PHARYNGITIS

SUBSEQUENT to the removal of infected tonsils, a granular pharyngitis may develop with symptoms of a constant sore throat, a sensation of a foreign body in the throat, or a collection of mucus clumps.

Lillie[1] observes that the best method of treatment on an empirical basis is the ingestion of iodides and suggests one tablet of ethyl diiodobrassidate chewed and swallowed from 2 to 4 times a day for a period of 5 days, decreasing as symptoms ameliorate.

Ethyl diiodobrassidate is available as Lipoiodine* in tablets free from local irritating effects and with a lower incidence of iodism in the usual dosage.

1. Lillie, H. I.: Archives of Otolaryngology, 24: Sept. 1936

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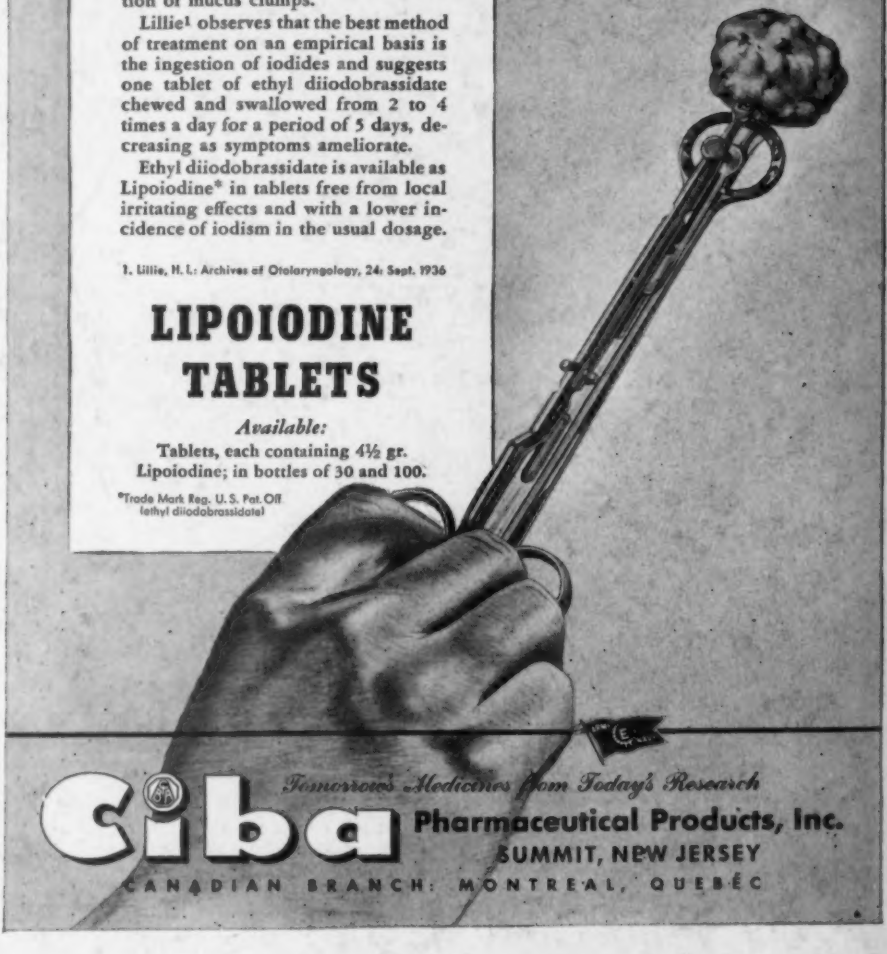
Tablets, each containing 4½ gr. Lipoiodine; in bottles of 30 and 100.

*Trade Mark Reg. U. S. Pat. Off. (ethyl diiodobrassidate)



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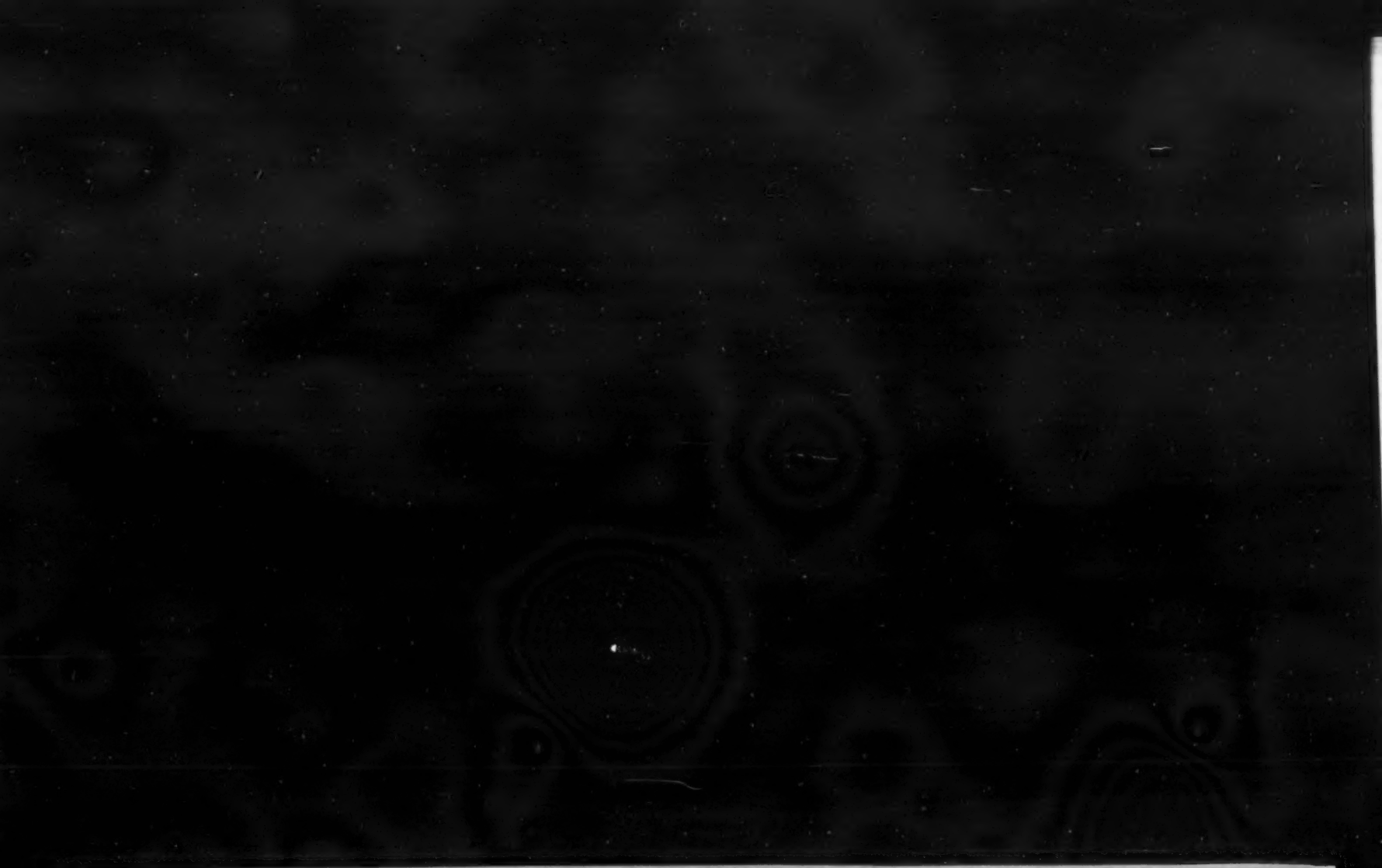

The Journal of Pediatrics

VOL. 24 APRIL, 1944 NO. 4

Original Communications

STUDIES OF AMINO ACID ADMINISTRATION

II. CLINICAL USES OF AN ENZYMATIC DIGEST OF CASEIN

ALEXIS F. HARTMANN, M.D., HARRY J. LAWLER, SC.D., AND CORNELIUS S. MEEKER, M.D.

ST. LOUIS, MO.

IN A previous report* it was shown that children fed a solution containing all of the "essential" amino acids ("Amigen"†), prepared by the digestion of casein with pork pancreas, can achieve a positive nitrogen balance. Our clinical experience with this solution now extends over a period of three years and includes its administration to more than 300 patients; it is now routinely used in this hospital as an adjunct to medical and surgical therapy as a means of preventing protein depletion. The present paper is devoted to description of some of the clinical uses of the preparation, together with discussions of its limitations, and the precautions that will avoid untoward reactions.

A. PREPARATION OF SOLUTIONS

"Amigen" was usually combined with glucose and other solutions for clinical use. The concentrations of components for any combination mentioned in this paper are those of the final solution; e.g., a solution containing 3⅓% "amigen," 3⅓% glucose, ⅓ "buffer" (frequently abbreviated "amigen"-glucose-"buffer" solution) was prepared by mixing equal parts of sterile (a) 10% "amigen" solution, (b) 10% glucose in distilled water, and (c) 1% lactic acid and .5% sodium lactate in distilled water. Ringer's or lactate-Ringer's (400 c.c. of frog Ringer's solution plus 10 c.c. of molar sodium lactate), was frequently mixed with "amigen" for parenteral use.

Acidified evaporated milk formulas were prepared by mixing (a) evaporated milk, (b) 1% lactic acid solution containing 15% corn

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

*Hartmann, Alexis F., Meeker, Cornelius S., Perley, Anne M., and McGinnis, Helen G.: J. PEDIAT. 20: 308, 1942.

†Supplied through the courtesy of the Mead Johnson & Co.

syrup, and (c) sterile water, the amount of water being adjusted so that the desired concentration of milk was achieved.

"Enriched" plasma was obtained by feeding blood donors one-half pint of "whipping" cream (38% butterfat) from four to five hours before withdrawal of blood. Extremely high levels of vitamin A may be obtained in such plasma by feeding concentrated preparations of fish liver oils with the cream. To the resultant high fat plasma may be added synthetic vitamin B complex, vitamin C, and vitamin D in propylene glycol (.1 to .2 c.c.) and glucose. The resultant product contains all of the known vitamins. It is given intravenously immediately after mixing.

B. ILLUSTRATIVE CASE HISTORIES

"Amigen" solutions were used in the treatment of a wide variety of diseases, as summarized in Table I. Common to all of the children was an inability to derive adequate nutrition from natural foods taken by mouth. The solution of amino acids was given primarily to prevent loss of body protein. To illustrate in some detail the manner in which the administration of this solution has come to form an integral part of our therapy in various diseases, several cases have been selected for presentation herein.

TABLE I

SUMMARY OF 173 CASES IN WHICH CASEIN DIGEST ("AMIGEN") WAS USED (TO NOVEMBER, 1942)

	ORALLY	PARENTERALLY
Bacillary dysentery (organism identified in 15 cases, unidentified in 20)	33	3
"Parenteral" diarrhea (with various infections in 36 cases; cause not determined in 16)	42	3
Ulcerative colitis	3	1
Pyloric stenosis	16	4
Intussusception	8	3
Stricture of esophagus	1	1
Atresia of esophagus		2
Wilm's tumor	1	
Spina bifida	1	
Anomaly of the nasopharynx		1
Incomplete rotation of cecum	1	1
Meningitis, encephalomyelitis		4
Pneumonia	2	3
Tetanus		1
Rabies		1
Celiac syndrome	7	
Pancreatic fibrosis, proved at autopsy	2	2
Pancreatic fibrosis, possible	3	2
Malnutrition (marasmus)	3	1
Allergic eczema	2	
Exfoliative dermatitis (rectal clysis—1)		
Aspiration of amniotic fluid	1	
Lymphoid leucemia		1
Chronic glomerulonephritis	6	5
Nephrosis	1	1
Prematurity (including diarrhea in the premature)	9	3

1. *Bacillary Dysentery.*—G. F. M., 22 months old, 8.8 kg., was admitted at 2:00 A.M. on July 10, 1942, with a history of watery diarrhea for nine days, fever for six, vomiting for three, blood in at least one stool, on July 8. Treatment at home had been ineffective. She was poorly developed, emaciated, markedly dehydrated, semicomatose, and her respirations were Cheyne-Stokes in type; moist râles were heard throughout the lungs. Her temperature was 39.2° C.; serum CO_2, 32.5 vol. %; W.B.C., 25,000. On culture, the Hiss-Park strain of *Bacillus dysenteriae* was recovered from the stools.

Immediate therapy consisted of 30 c.c./kg. of ⅙ M. sodium lactate intravenously and 30 c.c./kg. mixed with 40 c.c./kg. of Ringer's subcutaneously. Sodium sulfadiazine, .1 Gm./kg., was then given intravenously. For the first thirty hours only water, sulfadiazine, .2 Gm./kg./day, and sulfasuxidine, .25 Gm./kg./day, were given by mouth; 250 c.c. of 5% "amigen"—5% dextrose solution and 140 c.c. of whole blood were given intravenously, and 800 c.c. of lactate-Ringer's subcutaneously. The child's temperature fell to normal after twenty-two hours.

On the second day feedings of 3⅓% "amigen"—3⅓% dextrose—⅓ "buffer" solution, 30 c.c. every two hours, were begun; the amount given at each feeding was increased daily, 120 c.c. being given every two hours on July 15. On this regime the stools were at first profuse and watery, but became less frequent and less profuse until there were only three on July 15. She was placed on an acid skim milk formula, and the stools became normal the following day. Chemotherapy was then discontinued; she improved quickly and was discharged on July 20.

Therapy in this type of case is directed at:

(a) Relief of dehydration and acidosis. This is accomplished promptly and safely with ⅙ M. sodium lactate solution and Ringer's or lactate-Ringer's. Blood volume is thus increased, serum bicarbonate and extracellular fluid electrolyte replaced, ketosis abolished, and renal activity restored.

(b) Restoration of normal erythrocyte and protein values in the blood by prompt transfusion with whole blood.

(c) Bacteriostasis. Sulfadiazine is used partly because it has some effect on some strains of dysentery bacilli, but chiefly because severe diarrhea in infants is very frequently accompanied by parenteral infection. Sulfasuxidine is included for clinical experimentation.

(d) Resting the gastrointestinal tract. Only water or "buffer water" is given until the child is well hydrated, has ceased vomiting, and has some improvement in the diarrhea. This usually takes about twenty-four hours but sometimes longer as in this severe case. During this period parenteral administration of "amigen"-glucose-and lactate-Ringer's solution will prevent dehydration, ketosis, utilization of body protein, and recurrence of acidosis.

(e) Resumption of enteral feedings, using small amounts of "amigen"-dextrose-"buffer" solution. This is well tolerated, leaves no

residue, and tends to keep the upper parts of the gastrointestinal tract normally acidic. The amounts are gradually increased; by the second or third day, small amounts of acidic evaporated milk formula are alternated with the synthetic mixture. If improvement continues, the formula is gradually increased to one suited to the child's needs.

2. *Prematurity and Diarrhea.*—Baby J. L. S., 2 months old, 2.45 kg., had weighed 2.05 kg. at birth; he nursed very weakly; complementary formulas had been tried with poor results. For a week before entry he had vomited many feedings. On admission, June 14, 1942, he was markedly dehydrated and emaciated; serum CO_2 content was 36 vol. %. No focus of infection was found.

Dehydration, acidosis, starvation, and anemia were treated with 30 c.c./kg. of ⅙ M. sodium lactate intravenously and 30 c.c./kg. more, mixed with 40 c.c./kg. of Ringer's subcutaneously; 50 c.c. of blood and 50 c.c./kg. of Ringer's subcutaneously; 50 c.c. of blood and 50 c.c. of 10% glucose intravenously; and 200 c.c. of Ringer's subcutaneously. Feeding an acid evaporated milk formula was attempted, but he quickly developed a marked diarrhea. Sulfadiazine, .2 Gm./kg./24 hours, and sulfasuxidine, .25 Gm./kg./24 hours, were given; the gastrointestinal tract was rested by a twelve-hour period, during which only water was given, and then 15 c.c. of the "amigen"-glucose-"buffer" mixture was given every two hours for twelve hours; the amounts of this were gradually increased, 2,430 c.c. being fed during the next five days. To supplement the oral feedings, he was given 240 c.c. of 5% glucose-5% "amigen" solution and 100 c.c. of blood intravenously; 690 c.c. of 3⅓% "amigen"-3⅓% glucose-⅓ lactate-Ringer's solution were given subcutaneously. An intake of about 80 calories/kg./day was thus maintained with synthetic mixtures, and no weight was lost. Vitamin B complex was given intramuscularly. During this five-day period the diarrhea was slowly controlled, and dehydration and acidosis were alleviated.

He was then placed on slowly increasing amounts of an acidified evaporated milk formula and did fairly well for the next ten days. On July 3, however, bloody diarrhea suddenly recurred. A ten-hour period without food, followed by feedings of "amigen"-glucose-"buffer" mixture, 30 c.c. every two hours, controlled the diarrhea within twenty-four hours. On July 6 he was again placed on the acid milk formula and from then until discharge on July 15 improvement was steady.

Therapy in this case was similar to that outlined in the previous one and is an example of the value of parenteral feeding during a protracted period of diarrhea. It is our impression that such feeding will prove of definite value in maintaining the nutrition of premature infants, even in the absence of diarrhea, for their high metabolic rates and great needs for food are quite in contrast with their insufficiently developed eating and digestive mechanisms.

3. *Intussusception.*—Baby E. K., 4 months, 6 kg., entered on Feb. 4, 1942, with this history: vomiting and constipation for two and one-half

days; apparent attacks of abdominal pain, one day; with enema, blood but no stool was obtained. He was well nourished but moderately dehydrated; the abdomen was distended and tense; a mass was palpated in the right iliac fossa; his temperature was 37.7 C.; W.B.C., 12,450; R.B.C., 3.7 million. After administration of lactate-Ringer's subcutaneously and glucose and .1 Gm./kg. of sodium sulfadiazine intravenously, laparotomy was performed. An intussusception of about nine inches of ileum into the colon was found; upon reduction it was found to start at a Meckel's diverticulum. The ileum was dark, friable, and of questionable viability; no further surgery was attempted.

Postoperatively, sodium sulfadiazine, .4 Gm./kg./day, was given intravenously for three days; then sulfadiazine, .25 Gm./kg./day, orally for three more. Wangensteen suction and oxygen were used to prevent distention, and he was fed parenterally for the first two days with 900 c.c. of "amigen"-glucose-lactate-Ringer's solution and 120 c.c. of blood. On February 7 feedings of "amigen-" glucose-"buffer" solution, 30 c.c. every two hours, were started. On February 9 these were alternated with acidified evaporated milk formula, 30 c.c. of the latter being fed every four hours; larger amounts were then given, until February 16, when the synthetic feedings were dropped. On this regime he slowly improved; there was blood and pus in the stools for three postoperative days, and they were diarrheal for two more but normal thereafter. His temperature averaged 39° C. for eleven days, but then returned to normal until February 21, when bilateral otitis media was discovered. After bilateral myringotomy the ears drained for three days.

Starting on February 26 he vomited intermittently for four days; again all the signs of intestinal obstruction developed. After administration of 350 c.c. of 8% "amigen"-7% glucose solution and sodium sulfadiazine, .1 Gm./kg., a second laparotomy was done. Multiple dense adhesions of the ileum were found and a large mass of bowel had to be resected. He stood the prolonged procedure poorly; 200 c.c. of blood and 250 c.c. of 5% glucose were given during the operation; when returned to the ward he was in shock. Blood, 110 c.c., was then given, and a continuous intravenous drip of 1,000 c.c. of 5% "amigen"-5% glucose ran overnight; Wangensteen suction and oxygen were again used to prevent distention. By morning he was in surprisingly good condition. As before, small, frequent feedings of "amigen"-glucose-"buffer" solution were given for two days, supplemented by 685 c.c. of 8% "amigen"-7% glucose solution subcutaneously and 200 c.c. of "enriched" plasma intravenously. As he improved, small feedings of acidified milk were alternated with the synthetic food; the amounts were increased over the next five days, and then the synthetic feedings were omitted.

On March 21 the signs of intestinal obstruction appeared for the third time; conservative therapy was tried. Wangensteen suction re-

lieved the distention, then small frequent feedings of "amigen"-glucose-"buffer" solution were given for four days. There was marked improvement. Acidified evaporated milk was again fed, without difficulty, and thereafter the amounts were slowly increased. Supplementing oral feedings, 1,700 c.c. of 8% "amigen"-7% glucose solution were given subcutaneously during the first five days of this episode.

Convalescence was slow, but on discharge May 24 the child was on full formula and steadily gaining weight.

In this case it was assumed when the intussusception was reduced that there would be peritonitis and that the nonviable ileum would have to be resected at some future date. With the aid of chemotherapy and parenteral feeding he was carried along until there was sufficient healing of the small bowel so that safe excision of the obstruction became possible.

The use of "amigen"-glucose-"buffer" solution postoperatively and in the handling of the third episode of obstruction without operation illustrates the value of this solution in the restoration of intestinal function.

4. *Pyloric Stenosis.*—Baby G. A. R., 2 months old, 3.6 kg., entered on Feb. 5, 1942, with a history of intermittent projectile vomiting since the age of 2 weeks and acute illness for three days. On admission he was markedly dehydrated and emaciated; the skin was ashen gray; large peristaltic waves could be seen in the region of the stomach, and a pyloric tumor was felt just under the edge of the liver. Temperature was 39° C.; serum CO_2, 92 vol.%; serum chloride, 445 mg./100 c.c.

Dehydration, alkalosis, anemia, and starvation were relieved over the next three days by administration of parenteral fluids, including 550 c.c. of Ringer's, 400 c.c. of 10% glucose, 100 of 10% "amigen," and 80 c.c. of blood. An acidified evaporated milk formula was fed but was usually projectilely vomited. On laparotomy, Feb. 9, a pyloric tumor was found and sectioned longitudinally to the submucosa. The muscle was relatively vascular, and there was considerable oozing of blood, but no sutures were used.

Postoperatively, feedings of "amigen"-glucose-"buffer" solution were given, 30 c.c. every two hours for twelve hours, then 45 c.c. similarly for the next twelve hours. On February 10 he was placed on an acid milk formula, the amounts being slowly increased from 30 c.c. every three hours to full formula. Recovery was slow but relatively uneventful; there was no vomiting. He was discharged on March 1, gaining weight.

In this case the preparation of the patient for surgery by the parenteral administration of fluids undoubtedly rendered him a much better surgical risk and was partially responsible for the uneventful recovery.

5. *Peritonitis.*—C. E. B., a 3-year-old girl weighing 13.6 kg., was admitted on Dec. 29, 1941, acutely ill and moderately dehydrated; temperature was 39.6° C.; W.B.C., 17,500. Her abdomen was distended;

there was generalized muscle spasm, more prominent on the right, and pain referred to the umbilical region. After preparation with subcutaneous glucose in Ringer's and intravenous sodium sulfadiazine, .1 Gm./kg., the abdomen was opened; a generalized primary peritonitis was found. Purulent fluid was removed and the wound closed. The fluid grew a pure culture of type I pneumococci.

Chemotherapy with sulfadiazine, .2 Gm./kg./24 hours (maintained for the next twenty-two days) was continued, and 100,000 units of type-specific rabbit antiserum were given subcutaneously. Wangensteen suction and oxygen for the next twenty-four hours relieved distention. An intravenous drip was started and continued for the next three days; she received 4,850 c.c. of fluid during this period, including 2,400 c.c. of 10% "amigen," 1,225 c.c. of 10% glucose, and 1,225 c.c. of Ringer's. An intake of 35 cal./kg./24 hours was thus provided. On January 2 a thrombophlebitis developed, and parenteral feedings were stopped (details of this reaction are given later in this paper) and oral feeding with small amounts of milk begun. By the fourth postoperative day abdominal signs and symptoms were minimal and her temperature was normal.

On January 7 her temperature again rose to 39° C., and there was localized tenderness and muscle guard in the left lower quadrant; an abscess was suspected. The localizing signs were gone in two days, and although she ran a low fever for five more days, no further surgery was necessary; the balance of the convalescence was uneventful.

6. *Pneumonia With Cardiac Decompensation.*—T. D. H., 3 months old, 5.5 kg., entered with a history of pertussis infection eight weeks previously, which had developed into bronchopneumonia; this had apparently responded to sulfonamide therapy. Three days before admission the pneumonia recurred. On admission, Jan. 15, 1942, he was cyanotic, had rapid grunting respirations, cough, choking, and high fever; the pharynx was inflamed and moist râles were heard throughout the chest; the heart and liver were greatly enlarged. The diagnosis was bronchopneumonia with cardiac decompensation.

He was placed in an oxygen tent and given intravenous sodium sulfadiazine, .2 Gm./kg./24 hours. Attempted feeding of a milk formula produced severe attacks of coughing and choking; twice he went into shock and was revived only with artificial respiration and intracardiac medication with caffein or coramine. On January 17 feedings of "amigen"-glucose-"buffer" solution were tried; this was more adequately taken than milk, but the average amount taken per day during the next eleven days of severe illness was but 450 c.c. To supplement this, a total of 1,750 c.c. of 5% "amigen"-5% glucose solution was given subcutaneously; 100 c.c. of plasma and 120 c.c. of blood were given intravenously. The daily intake averaged about 40 calories/kg./day during this period, but the child lost only 300 Gm. and clinically improved. Sulfadiazine .2 Gm./kg./day, was given for the first two weeks.

On January 25 his temperature was down to normal, and on January 28 he was taken from the oxygen tent. An acidified evaporated milk formula was then started, without difficulty, and the amounts given were quickly increased to full caloric requirements. The rest of the convalescence was slow, but on discharge, February 25, the heart shadow had decreased to about normal size, the lungs were clear, and he was beginning to gain weight.

Attempted milk feedings were followed twice by collapse in this critically ill infant. Yet he was able to take about a pint of "amigen"-glucose-"buffer" solution orally each day, and subcutaneous administration of "amigen-glucose" solution permitted fairly adequate maintenance of nutrition during an eleven-day period.

7. *Tetanus.*—M. E. W., a 6-year-old girl, entered on July 9, 1942, in a state of marked spasticity involving all extremities, abdominal, neck, and facial muscles; during intermittent paroxysms there was opisthotonus, trismus, and risus sardonicus. The primary wound was not found. She was given 100,000 units of antitoxin and was sedated with 80 mg. of avertin. This sedation sufficed for only a short time; that night, during a paroxysm, she bit her tongue. Heavier sedation was then effected and maintained fairly continuously for the next two weeks, using from 3 to 8 Gm. of avertin and from 1.5 to 4.5 gr. of sodium phenobarbital each day. In spite of this and a mouth gag, she again bit her tongue on July 15; her temperature rose to 39° C. The next day the fever continued; her breathing was very labored, and many râles and transmitted rhonchi were heard in the chest; the tongue was bleeding and there was blood and mucus in the throat. Tracheotomy was performed; she coughed up clotted blood from the trachea, and more blood was aspirated from the bronchi. Fever continued for five days postoperatively despite intravenous chemotherapy; intermittently blood was suctioned from the trachea.

For this first fourteen days the child's feeding was entirely by intravenous drip, 20,750 c.c. of 33⅓% "amigen"-3⅓% glucose-⅓ Ringer's solution, 1,250 c.c. of 10% glucose, and 370 c.c. of blood being given; vitamin B complex and vitamin C were given parenterally. Her intake averaged about 23 calories/kg./day; in spite of tracheotomy, fever, and intermittent paroxysms, she lost only one-half pound in the two weeks.

On July 23 her condition was so improved that a nasal tube was passed. She was given the dextrose-"amigen"-Ringer's mixture by tube for forty-eight hours; then milk was introduced in gradually increasing amounts. For the next eight days milk feedings were alternated with the synthetic mixture; the latter was discontinued on August 1 when the nasal tube was withdrawn. On August 3 her condition was such that sedation was discontinued; physiotherapy was begun to alleviate residual spasticity. By August 25, she was able to walk

without aid and on discharge, on September 1, there was only slight residual spasticity in the extremities.

The therapy in this case was primarily that of sedation, 99.2 Gm. of avertin, 72.5 gr. of phenobarbital, 9.75 gr. of seconal, and 12.5 Gm. of chloral hydrate being used, chiefly in the first two weeks of illness. Passive transfer of immunity, by parenteral administration of 100,000 units of antitoxin, was thought to be of lesser significance because the toxin had already attained the neurons.

The maintenance of nutrition was the next problem. Oral feedings being obviously impossible, parenteral feeding of glucose, amino acids, and vitamins was necessary for two weeks, the longest period during which this has been necessary for any child. That it was successful was shown by the fact that, despite the somewhat stormy course of her illness, she lost but one-half pound in this period.

8. *Diarrhea in Chronic Glomerulonephritis.*—Two children, D. Y., aged 3 years, and H. B., aged 11 years, both in a nephrotic stage of chronic glomerulonephritis and both living in the hospital for long periods, simultaneously developed slowly increasing anorexia and mild diarrhea starting on about Sept. 18, 1942. No pathogenic organisms were cultured from their stools, no focal infections were found, and the diarrhea did not respond to chemotherapy.

After two weeks of diarrhea one of them, D. Y., began to vomit his food; his vomiting steadily grew worse during the next weeks until he vomited almost everything taken by mouth. On October 8 he was given 320 c.c. of 20% glucose and 160 c.c. of 5% "amigen"-5% glucose solution intravenously. During the next seven days ten injections of the latter solution were given, totalling 2,120 c.c. Vitamins A, D, and B complex were given intramuscularly on October 10 and 12. The result of this therapy was that the vomiting stopped almost immediately. The diarrhea stopped and his appetite improved on the third day. He ate well therafter, and the diarrhea did not recur.

The second child had diarrhea and anorexia for three weeks but did not vomit. He was given 3,300 c.c. of the same solution over the same period, and the same vitamins parenterally, with similar results; his appetite returned on the third day of treatment and diarrhea ceased on the fourth.

From experiences like these it seems reasonable to conclude that parenteral amino acids are probably of value in the maintenance of children who have such kidney lesions and are definitely worth a trial. However, we do not believe that they have been shown to have any beneficial effect on the primary pathologic process. The plasma proteins were not appreciably changed during this period.

C. PARENTERAL ADMINISTRATION

The original solutions of "amigen" as used by Hartmann and coworkers (1942) were found to be unsuited to routine parenteral adminis-

tration to children because of untoward reactions, in spite of the fact that the casein digest was stated to be pyrogen-free and nonantigenic. In considering those results, it was noted that the solutions used were distinctly acidic, the pH of the one furnished by the manufacturers being 4.5. In the hope that a more alkaline solution might be tolerated parenterally, the makers were asked to furnish a solution titrated to as high a pH as possible without causing precipitation of any of the amino acids. They prepared a new 10% solution with a pH of 6.5.

This solution was first tested in November, 1941, with 6-week-old laboratory rats. Each of four received 2 c.c. subcutaneously at the same site for nine consecutive days; on autopsy the day after the last injection no gross evidence of reaction could be seen. Eight other rats received it intraperitoneally; four received 2 c.c. daily, four others 4 c.c. daily each, for nine consecutive days; on autopsy the day after the last injection no macroscopic evidence of reaction was found.

Small amounts of the solution (10 to 20 c.c.) were then given subcutaneously to two athreptic infants on consecutive days. No adverse reaction occurring, one (H. E. R., Table III) was given 160 c.c. at one site; the skin flushed, but the color disappeared with the absorption of the fluid. Three nephritic children, all edematous, were then given injections of 10 c.c. subcutaneously; no adverse reaction occurring, each was given 25 c.c. at the same site on each of three consecutive days. They complained of pain during the distention of the skin, but this disappeared after a few minutes; the site remained flushed until the fluid was absorbed. One of the three complained of tenderness to pressure at the site the day after the last injection. It was apparent that this solution of "amigen" was less irritating than the more acidic ones had been, and parenteral use on a wider scale became possible.

Upon request, the manufacturers also prepared a 15% solution of "amigen," pH 6.5. Upon limited trial, this was found to be too locally irritating for subcutaneous use; 10 c.c. produced a sharp burning sensation and local hyperemia; the pain persisted from five to ten minutes. After absorption of the fluid, however, there was no residual reaction from single injections.

Intravenous Use.—

A. By syringe: A total of 2,085 c.c. of "amigen," as the 10% solution (pH 6.5) or mixed with other solutions, was given intravenously in short periods of time to nine children up to November, 1942, as outlined in Table II, *A*. The following reactions occurred:

1. Baby S. J. H. received one-half lot of 150 c.c. of 3⅓% "amigen"-3⅓% glucose-⅓ Ringer's solution without reaction. After twelve hours of refrigeration, the rest was injected, without warming. After 65 c.c. had been given there was a massive edema of the face and head; simultaneously there was copious secretion of serous fluid from the mucous membranes of the nose. The abdomen became distended and the skin of the entire body turned an orange color; respi-

TABLE II

INTRAVENOUS USE OF "AMIGEN," pH 6.5

(NOVEMBER, 1941, TO NOVEMBER, 1942)

CASE	AGE	KG.	SOLUTION	AV. NO. C.C. INJECTED	TOTAL	FASTEST, G/KG./MIN.
A. *By Syringe*						
1. L. J. A. Premature, diarrhea	3 wk.	1.7	5% amigen 5% glucose	55	110	.35
2. J. I. S. Premature, diarrhea	2 mo.	2.5	5% amigen 5% glucose	48	240	.10
3. C. L. S. Premature, diarrhea	13 days	1.5	5% amigen 5% glucose	40	40	.27
4. S. J. H. Parenteral diarrhea	5 mo.	3.5	3⅓% amigen 3⅓% glucose ⅓ Ringer's	75	445	.16
5. A. W. S. Pyloric stenosis	6 wk.	3.3	3⅓% amigen 3⅓% glucose ⅓ Ringer's	102	205	.21
6. E. K. Intussusception	4 mo.	6.0	8% amigen 7% glucose	95	285	.30
7. J. A. M. Pancreatic fibrosis	3 mo.	2.5	8% amigen 10% glucose	46	460	.44
8. R. L. S. Glomerulonephritis	3 yr.	16.8	5% amigen 5% glucose	75	150	.15
9. C. F. H. Glomerulonephritis	5 yr.	18.2	15% amigen	75	150	.41
B. *By Intravenous Drip*				NUMBER OF DAYS		
1. W. E. T. Pancreatic fibrosis ?	2 yr.	10.0	3⅓% amigen 3⅓% glucose ⅓ lactate-Ring.	2	600	.022
2. M. E. W. Tetanus	6 yr.	18.7	3⅓% amigen 3⅓% glucose ⅓ Ringer's	14	20,750	.0018+
3. K. L. S. Encephalomyelitis	8 yr.	17.0	3⅓% amigen 3⅓% glucose ⅓ Ringer's	1	750	.05
4. E. K. Intussusception	4 mo.	6.0	5% amigen 5% glucose	1	1,000	.008
5. G. F. M. Dysentery	22 mo.	8.8	5% amigen 5% glucose	1	250	?
6. C. E. B. Peritonitis	2 yr.	13.6	Various mixtures of 10% amigen (2,400 c.c.) 10% glucose, with Ringer's or lactate-Ringer's	3	4,850	.0046+
7. H. B. Glomerulonephritis	11 yr.	32.7	5% amigen 5% glucose	8	3,300	.0102
8. D. Y. Glomerulonephritis	3 yr.	13.8	5% amigen 5% glucose	25	3,920	.0161
9. C. J. R. Nephrosis	6 yr.	25.0	5% amigen 5% glucose	6	1,620	.0146

ration slowed almost to a stop. With adrenalin there was prompt response, although the respiration remained slow and irregular for about five hours. The edema and orange color disappeared in about one and one-half hours.

The contents remaining in the syringe were seen to be cloudy with tiny white flakes or crystals; unfortunately the fluid was discarded. Since much more concentrated solutions (8% "amigen," 7% glucose) have been refrigerated for weeks without precipitation, it seems likely that this precipitate represented contamination with foreign material. The exact cause of this reaction was not determined.

2. R. L. S and C. F. H. (Cases 8 and 9, Table II, *A*) each received two rapid injections. Both flushed markedly, complained of warmth, and each child vomited after one of the injections.

It is of definite interest that the reactions noted in the latter cases, to be expected when amino acid solutions are administered too rapidly to children, apparently did not occur when similar injections were given to infants. The oldest of these was but 5 months; possibly the vasodilatory response to amino acids involves a mechanism that is relatively inactive in the young infant.

B. By Intravenous Drip: A total of 34,840 c.c. of various solutions of "amigen" was given to nine children as outlined in Table II, *B*, resulting in the following reactions:

1. After nine hours of attempts to secure a needle in some vein of child C. E. B., the left saphenous vein was surgically exposed and a needle ligated into it. For the next fifty-eight hours a continuous drip of 4,850 c.c. of various solutions, including 2,400 c.c. of 10% "amigen," was maintained. A thrombophlebitis then developed and the drip was stopped. During the next seven days the phlebitis cleared, without sequelae. Chemotherapy was given throughout the period.

This reaction probably could have been prevented had the use of any single vein been restricted to a shorter period.

2. Accompanying each of forty-nine injections given at a rate of .01 Gm. of "amigen"/kg./minute or faster, there was some facial flushing and a feeling of warmth. Nausea and vomiting have been observed twice, when the fluid was injected immediately after a paracentesis had been done.

This is, again, the reaction to the rapid administration of amino acids. As yet, we have not sufficient data to enable us to estimate accurately the rate at which they may be given intravenously without causing any reaction; probably it is less than .01 Gm./kg./minute.

Subcutaneous Use.—Solutions as concentrated as 5% "amigen" and 5% glucose were well tolerated. Up to November, 1942, 8,365 c.c. of this had been given to fifteen infants (see Table III) subcutaneously without reaction. One infant (T. D. H., Case 8 in Table III) received over 300 c.c. a day for five consecutive days.

TABLE III

SUBCUTANEOUS USE OF "AMIGEN," pH 6.5

CASE	AGE	KG.	SOLUTION	AMOUNT (C.C.)	NUMBER OF DAYS
1. J. W. H. Pancreatic fibrosis	4 mo.	5.6	a. 5% amigen 5% glucose	325	2
			b. 8% amigen 7% glucose	6,000	20
2. W. T. B. Atresia of esophagus	5 days	2.0	8% amigen 7% glucose	150	1
3. E. K. Intussusception	4 mo.	6.0	a. 8% amigen 7% glucose	2,550	7
			b. 5% amigen 5% glucose	600	2
			c. 3⅓% amigen 3⅓% glucose ⅓ lactate-Ring.	900	2
4. J. A. M. Pancreatic fibrosis	3 mo.	2.5	Many, up to 10% amigen 10% glucose	1,550	6
5. H. E. R. Anomaly, nasopharynx	3 mo.	3.2	a. 10% amigen	190	3
			b. 8% amigen 5% glucose	500	1
6. K. M. V. Bronchopneumonia	3 mo.	8.6	5% amigen 5% glucose	1,500	3
7. J. M. P. Lobar pneumonia	10 mo.	5.9	5% amigen 5% glucose	2,000	4
8. T. D. H. Bronchopneumonia	3 mo.	5.5	5% amigen 5% glucose	1,750	5
9. J. L. R. Intussusception	5 mo.	6.7	5% amigen 5% glucose	500	1
10. L. M. Peritonitis	15 mo.	10.5	5% amigen 5% glucose	140	1
11. G. A. R. Pyloric stenosis	2 mo.	3.6	5% amigen 5% glucose	200	1
12. D. M. G. Pyloric stenosis	3 wk.	2.4	5% amigen 5% glucose	200	1
13. L. J. S. Dysentery	11 mo.	8.9	5% amigen 5% glucose	400	1
14. L. P. Parenteral diarrhea	1 yr.	7.3	3⅓% amigen 3⅓% glucose ⅓ Ringer's	300	1
15. M. L. N. Malrotation, cecum	10 days	2.9	3⅓% amigen 3⅓% glucose ⅓ Ringer's	195	3
16. E. J. Stricture, esophagus	2 yr.	10.0	3⅓% amigen 3⅓% glucose ⅓ Ringer's	650	1
17. L. J. A. Premature, diarrhea	3 wk.	1.7	Similar, but with lactate-Ringer's	70	1
18. J. L. S. Parenteral diarrhea	2 mo.	2.5	Similar, but with lactate-Ringer's	690	4

A stronger solution, containing 8% "amigen" and 7% glucose was given to three children. In one case (E. K., Case 3 in Table III) a total of 2,550 c.c. of this was given over a period of seven days, all in the anterior surface of the thighs. The subcutaneous tissues underwent a soft induration. This disappeared several days after discontinuance of the fluids. Probably the use of several sites, alternately, could have prevented this reaction.

Another infant, L. M., 10 months old, suffering from aplastic anemia, bilateral suppurative otitis media, and chronic dysentery (Hiss-Park) for five weeks was given repeated hypodermoclyses of 600 c.c. of a mixture of equal parts of 10% "amigen," 10% glucose, and lactate-Ringer's without reaction. Because it was desired to give her greater quantities of food parenterally, she was given 800 c.c. of 8% amigen, 7% glucose (NaCl content about .4%) subcutaneously. The first 400 c.c. flask was absorbed well over a period of about six hours. The second 400 c.c. was not well absorbed; it was mistakenly permitted to flow under the skin and accumulate as a large area of edematous tissue over the thighs and lower abdomen. The following morning the baby was seen to be critically dehydrated with rapid shallow respiration, ashen pallor, and sunken eyes; the local "pocket" of fluid had evidently dehydrated the rest of the body. On intravenous administration of glucose and plasma, the infant's condition improved and the edema subsided, so that it was again possible to give subcutaneous fluids about twelve hours later.

Reactions similar to this one have occurred on subcutaneous administration of solutions of crystalloids to two other athreptic infants. We believe, therefore, that when such solutions are given to infants they should be carefully watched. If a large pocket accumulates under the skin and the solution does not flow in, subcutaneous administration should be stopped. Because low plasma proteins and poor peripheral circulation are the probable causes of such poor absorption, the intravenous administration of plasma and dextrose is indicated.

The most concentrated solution given contained 10% "amigen" and 10% glucose; 300 c.c. of this was given to baby J. A. M.; absorption was very slow, and some was still unabsorbed twenty-four hours later. This may have been related to tissue anoxia as well as to the concentration of the solution, for the child was markedly cyanotic. Beyond the usual local flushing, there was no evidence of adverse reaction.

In general, the most widely used solution has been that obtained by mixing equal parts of 10% "amigen," 10% glucose, and lactate-Ringer's. This is usually concentrated enough for parenteral feeding, and we have yet to have an undesirable reaction to its subcutaneous use in subjects not severely dehydrated.

Intraperitoneal Administration.—Five intraperitoneal injections of "amigen" solution have been given, as outlined in Table IV. Two injections were given to an infant, H. E. R.; after the first one, of 50

TABLE IV

INTRAPERITONEAL USE OF "AMIGEN"

CASE	AGE	KG.	SOLUTION	AMOUNTS (C.C.)	COMMENTS
1. H. E. R. Anomaly, nasopharynx	7 mo.	3.2	10% amigen	a. 50 b. 40	Reaction ? No reaction
2. R. L. S. Glomerulonephritis	3 yr.	16.8	10% amigen 15% amigen	100 100	All given after paracentesis; flush, vomiting
3. C. F. H. Glomerulonephritis	5 yr.	18.2	15% amigen	100	

c.c., his temperature rapidly rose 2° C. in the next seven hours. This temperature continued for the next nine days, subsiding only after bilateral myringotomy. Since it was thought that the fever was related to the infections rather than to the "amigen" injection, a second injection of 40 c.c. was then given. There was no reaction. Three other injections were given to two other children through the same needle that had just been used for paracentesis. In all three cases the child's face and shoulders flushed deeply, and each vomited small amounts.

These results apparently indicate that the solution is very rapidly absorbed from the peritoneum, for the reactions are the same as those occurring after rapid intravenous administration. Considering the ease of subcutaneous administration, however, the intraperitoneal route will probably not be widely used.

DISCUSSION

The use of amino acid solution either orally or parenterally makes it possible to prevent or reduce loss of body protein by children who are unable to derive adequate nutrition from natural foods taken by mouth. When used with glucose and vitamins it probably makes possible complete parenteral feeding over relatively long periods as has been shown in Case 7 in the text (tetanus). In combination with glucose and "buffer" solution, it is of value in the resumption of enteral feedings in cases of intestinal irritation such as dysentery, "parenteral" diarrhea, peritonitis, and postoperative conditions (see Cases 1 to 5 in text). In the presence of actively functioning kidneys, its salt content makes it of some value in the maintenance of acid-base balance (per cent in the 10% solution, pH 6.5; Cl, .2; Na., .29; Ca, .01; Mg., .005; Fe, .002; and P, .09).

To avoid undesirable reactions such as those outlined previously in this paper, it is necessary to be aware of certain limitations both of the "amigen" solution itself and of technique of administration:

1. The pH 6.5 solution, although much less irritating than the more acidic solutions previously used, is still relatively more acidic than the body's fluids. Hence its parenteral use is probably not indicated in the presence of untreated acidosis and oliguria. This is especially true when intravenous administration is contemplated.

2. Solutions more concentrated than 3½% are hypertonic and may be locally irritating on that account. This has not proved to be a practical obstacle to the use of very much more concentrated solutions (see Tables II and III) subcutaneously without residual reaction. A safe rule to avoid local reactions is to discontinue administration at any site or in any vein which has been in use for twenty-four hours.

3. Too rapid intravenous administration in children first produces a facial flush and a sensation of warmth, then a spreading flush over the body, nausea, vomiting, and perhaps fever. To avoid this reaction, a slow intravenous drip is recommended; when the child's face begins to flush, the drip should be slowed. A rate below .01 Gm./kg./minute is probably best.

4. In infants the subcutaneous route is very much to be preferred to the intravenous one for these reasons: It is vastly easier technically and the fluid is absorbed at a rate roughly governed by the child's ability to handle it instead of by someone else's convenience.

5. Concentrated solutions are absorbed rather slowly subcutaneously. For example, 300 c.c. of 5% "amigen"-5% glucose solution is taken up from a two-needle hypodermoclysis by an infant in from three to eight hours, depending on the size of the infant and his hydration. When one considers that this represents about 120 calories, however, such an absorption rate seems to parallel that of a meal from the intestine, and hence seems no liability.

6. Severe dehydration or the presence of a very low plasma protein or a poor peripheral circulation *after* hydration is a contraindication to the subcutaneous administration of any solution of crystalloids such as the "amigen"-glucose mixtures. They tend to remain locally where injected and to withdraw water from the blood and tissues.

THE RELATION OF PANCREATIC ACHYLIA TO MECONIUM ILEUS

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THE relationship of pancreatic disease in the newborn infant to grossly abnormal meconium, which is responsible for intestinal obstruction, was indicated in 1905 by the studies of Landsteiner.[1] The cause of the lesion of the pancreas may be a congenital stenosis of the pancreatic ducts, as was demonstrated clearly by the studies of Kornblith and Otani[2] and, more recently, by Hurwitt and Arnheim.[3] When atresia or stenosis of the pancreatic ducts is not demonstrable, the obstruction appears to begin in the acini themselves because of an altered physical character of the acinar secretions which leads to duct obstruction and dilatation, atrophy of the parenchyma, and, finally, fibrosis of the pancreas.[4] The painstaking examination of the pancreas described by Kornblith and Otani[2] illustrates the type of study necessary for an accurate statement concerning the state of patency of the pancreatic ducts. Hurwitt and Arnheim[3] proved the existence of congenital stenosis of the pancreatic ducts for the second time in a patient with meconium ileus with the aid of serial sections. From embryologic studies they concluded that the cause of the stenosis was a focal developmental defect. Summaries of the recent literature and discussion of some of the problems involved may be found in the papers by Dodd,[5] Hurwitt and Arnheim,[3] Bronaugh and Lattimer,[6] Denzer,[7] Sobel,[8] and Kaufmann and Chamberlin.[9] It is the purpose of this paper to supply data concerning the relation of pancreatic enzymes to the altered physical state of meconium in patients with meconium ileus.

PRESENT STUDIES

Post-mortem examination of eighteen infants who presented the clinical picture of high intestinal obstruction caused by inspissated meconium revealed in each instance an obstructive lesion in the pancreas characterized by inspissation of secretions, dilatation of ducts, atrophy of acini, and fibrosis of the pancreas. The meconium seen either at operation or at autopsy was so sticky and mucilaginous in consistency that fingers and instruments were not easily extricated from the meconium after contact. Such physically altered meconium cannot be propelled through the bowel and is responsible for the intestinal obstruction (Fig. 1). Experiments were performed with the meconium taken

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These studies were conducted with the aid of the Ann Proctor Rice Fund of Harvard Medical School.

from thirteen patients at operation or at autopsy to study the effect of extracts of the pancreas upon the physical state of the meconium.* It was found that when this type of abnormal meconium from patients with meconium ileus was placed in a test tube containing saline solutions of pancreatin,† which varied from 1 to 10 per cent in strength, at a temperature of 37.5° C., the meconium was reduced within a short time to semifluid or fluid state. In general, the stronger solutions acted more

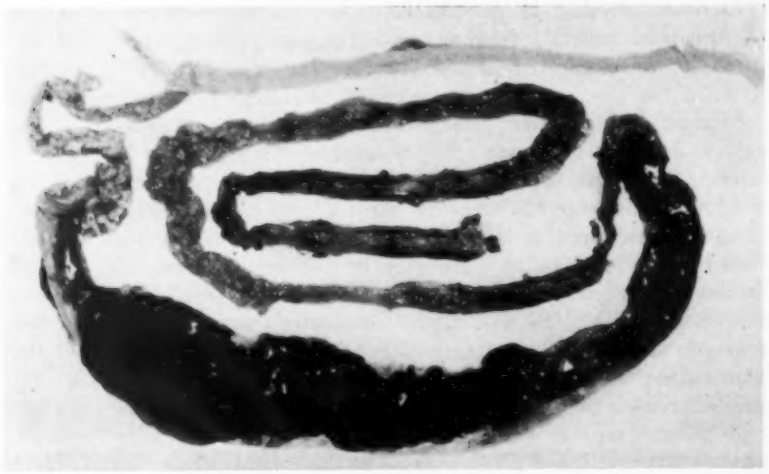

Fig. 1 (A-33-133).—Characteristic post-mortem picture of intestines in meconium ileus. The patient was a 2-day-old infant, one of twins, both of whom had meconium ileus. Note greatly distended small bowel, the ileal portion filled with mucilaginous meconium. The large intestine seen distal to the appendix is very much smaller than the ileum and jejunum.

quickly, although little difference was noted between the efficacy of the 5 and the 10 per cent solutions. A 1 per cent solution of pancreatin brought the abnormal meconium into a semifluid state usually in from two to four hours in contrast to from one to two hours required in most instances by the 5 per cent solution. Complete solution of the meconium to such a degree that no solid particles were visible was brought about in one instance (S-42-669) in 110 minutes by a 1 per cent as well as by a 5 per cent and a 10 per cent concentration of pancreatic extract (Fig. 2).

These observations suggested the possibility that inspissated meconium might be washed from the bowel by means of an enterostomy with pancreatic extracts used as a solvent. In four infants operated on by Dr. Robert E. Gross this was carried out with relief of the mechanical

*The assistance, in some of these experiments, of Dr. Charlotte Maddock, Dr. Harry Shwachman, and Mrs. Ruth Berman Pitt is gratefully acknowledged.

†Pancreatic extracts which were used in these studies and gave good results included Wilson U.S.P. Powder, Wilson Triple Strength Powder, Lilly Triple Strength Powder, Parke-Davis Panteric Capsules and Cenco Trypsin.

blockade of the intestine. A 1 per cent solution of pancreatin was employed on these infants. Death occurred several days to a few weeks later because of intercurrent infection. The clinical details will be reported elsewhere by Dr. Gross.

We have reported the results of analysis of duodenal drainage from a patient in whom intestinal obstruction caused by meconium ileus had

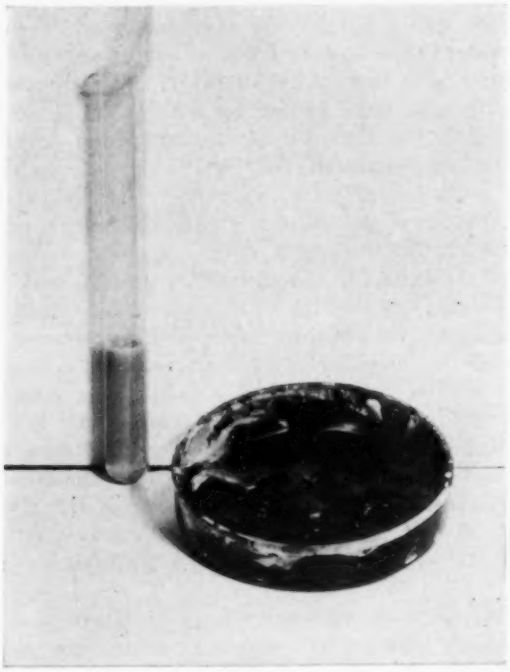

Fig. 2 (S-42-669).—Meconium in Petri dish removed during operation on infant 2 days old with meconium ileus. Some of this meconium was placed in a test tube containing a 1 per cent saline solution of pancreatic extract (pancreatin). Note complete dissolution of meconium which occurred in 110 minutes.

been relieved by washing the small intestine with 1 per cent saline solution of pancreatic extract through a catheter in the ileum.[10] When the patient had recovered from the intestinal obstruction at 3½ weeks of age, fluid was withdrawn from the duodenum over a period of two hours. There was no evidence of tryptic activity by either the viscosimetric method or the Andersen-Early modification of the Fermi method.[10] In one other instance the duodenal content was removed from a patient who had a typical story of meconium ileum and who died at the age of 5 days. The material was obtained from the duodenum within one hour after death. In this duodenal content no evidence of tryptic activity was demonstrable.*

*Dr. Harry Shwachman performed these analyses.

DISCUSSION

The causal relationship of pancreatic achylia, whether produced by congenital malformation of the pancreatic ducts or by intrinsic acinar and small duct obstruction to the altered physical state of the meconium in meconium ileus, appears proved by these data. The obstructive lesion of the pancreas responsible for meconium ileus may be present not only in the newborn infant, but also is found with regularity in infants under 1 year of age who have chronic pneumonia and severe nutritional failure and also in children over 1 year of age who have a type of nutritional failure closely resembling idiopathic celiac disease.[11, 12] In all three clinical groups histologic studies have led to the suggestion that interference with the entrance of the pancreatic enzymes into the duodenum results in pancreatic achylia which appears to play a primary role in the causation of those symptoms referable to the intestinal tract.[10, 11] Analysis of post-mortem studies on patients with pancreatic fibrosis has shown that in those in whom congenital malformation of the ducts is not the cause of the pancreatic achylia, and they are the majority of infants and children with this pancreatic disease, the process is really a systemic disease involving secretion-producing structures in many parts of the body, including the tracheal and bronchial glands, the salivary glands, and intestinal glands.[4] Pancreatic achylia, no matter how produced, is the common denominator in patients with meconium ileus and in those who live longer and who die of chronic pneumonia and severe nutritional failure. The time at which the pancreatic achylia occurs determines the nature of the clinical picture. If pancreatic achylia is present at birth, then the patient will be born with intestinal obstruction caused by inspissation of abnormal meconium.[4]

In the literature, references are made to instances of meconium ileus with no evidence of pancreatic disease.[9] It appears probable that in such instances a somewhat similar but fundamentally different condition is present. Inspissated meconium may be found in newborn infants with stenosis of the ileocecal valve or volvulus. In these patients the meconium is inspissated but is not nearly as viscid or mucilaginous in consistency as in patients with pancreatic achylia. The clinical problem is quite different from that in true meconium ileus; if the partial or complete obstruction to the intestinal tract is relieved, the inspissated meconium will offer no great difficulty to removal. In the case of meconium ileus caused by pancreatic achylia the physical state of the meconium precludes normal evacuation.

Doubt may be expressed, too, concerning the occurrence of true meconium ileus in newborn infants said to have liver disease or biliary obstruction in the presence of a normal pancreas. We have studied at autopsy thirty-four infants with congenital atresia of the bile ducts. In none was evidence of meconium ileus observed. A review of some of the reported instances of normal pancreas associated with true meconium

ileus might reveal previously unrecognized lesions in the acini. In recent years we have observed in patients with symptoms resembling the celiac syndrome, and in whom we have demonstrated pancreatic achylia during life, important obstruction in the acini and small ducts without any evidence of dilatation of the larger ducts or of pancreatic fibrosis. These represent, nonetheless, as completely obstructive lesions as may be found in the classical "cystic" fibrosis of the pancreas.[10]

Although the intestinal obstruction caused by altered meconium may be treated successfully by the use of pancreatic extracts, further difficulty may be encountered if the patient survives the neonatal period with the aid of such treatment. It will be necessary to continue the pancreatic substitution therapy as long as there is proof of pancreatic achylia if a severe failure of nutrition, such as that found in the celiac syndrome, is to be avoided. Of greater importance is the danger which may be encountered in those patients in whom the pancreatic lesion is but one of the manifestations of a systemic disease. If obstruction in many secretion-producing structures in the body is marked, death may occur because of respiratory disease or even of cirrhosis of the liver. This supposition is based upon the finding at autopsy of lesions involving many different secreting structures of the body in infants and children with pancreatic achylia and a clinical picture resembling celiac disease complicated by chronic penumonia. No infant with true meconium ileus caused by pancreatic insufficiency has lived more than several weeks, so that proof of this supposition is not available in patients in whom the first sign of pancreatic insufficiency is meconium ileus. There is no clinical method for determining which patient with meconium ileus will develop symptoms referable to other organs in the body and which will have the disturbance limited to the consequences of pancreatic achylia.

SUMMARY AND CONCLUSIONS

From the post-mortem examination of eighteen patients with meconium ileus, support is obtained for the original suggestion of Landsteiner, that in patients with meconium ileus an obstructive lesion of the pancreas is of importance. Pancreatic achylia, which may be anticipated from the histologic picture of the pancreas, was proved by actual analysis of the tryptic activity in the duodenal drainage of one living and one recently dead patient with meconium ileus. No evidence of tryptic activity in the duodenal drainage was noted in either case. Experiments performed both in vitro and in vivo with the altered meconium in patients with meconium ileus have shown that this material may be brought into a semifluid or fluid state by the action of dilute saline solutions of extracts of the pancreas. The application of these observations to the treatment of patients with meconium ileus has resulted in relief of the intestinal obstruction. Caution in prognosis should be exercised, however, for even when the intestinal obstruction

caused by altered meconium is relieved by the solvent action of pancreatic extracts, possible danger to the later welfare of the patient may still exist because of the nutritional consequences of pancreatic achylia or because the lesion of the pancreas is but one of many similar lesions involving a number of secreting structures in the body. Meconium ileus caused by pancreatic achylia should be differentiated from the clinically much less important inspissated meconium found in patients with partial or complete obstruction to the intestine in the neonatal period.

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POLYNEURITIS OF UNKNOWN ETIOLOGY IN CHILDHOOD

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THE two cases of polyneuritis first described by Guillain, Barré, and Strohl[1] in 1916, purporting to demonstrate a new syndrome, were characterized by (a) motor disturbances, (b) loss of tendon jerks, (c) preservation of cutaneous reflexes, (d) paresthesias, (e) tenderness on pressure of the muscles, (f) little change in electrical reactions, and (g) albuminocytologic dissociation in the spinal fluid. These changes are identical with those found in many types of polyneuritis.[2-4] According to Guillain,[5] the syndrome occurred in both sexes between the ages of 20 and 50 years but was rare in children and old persons. It has been particularly interesting to us, therefore, to find that seventeen cases diagnosed as Guillain-Barré syndrome in patients under 20 years of age had been treated in this clinic since 1934. This has afforded an opportunity for a critical review of the basis for such a diagnosis and to show that these are probably examples of polyneuritis traceable to a variety of causes. Since the time the original description of the syndrome appeared, cases have been reported from practically every country in the world.[6-25] At times the number of cases has reached epidemic proportions.

GENERAL CONSIDERATIONS

So many of these cases have now been described in patients under 20 years of age that Susman and Maddox[24] now characterize the syndrome as an apyrexial disease of childhood and adult life showing the signs originally described by Guillain and Barré as well as acellular hyperalbuminosis of the spinal fluid, absence of fever, a euphoric state in the presence of severe illness, slight, transient muscular atrophy, and complete recovery. These findings are likewise compatible with a diagnosis of polyneuritis,[2-4] but complete recovery is not always the case as will subsequently be pointed out.

ETIOLOGY

The exact etiology of the polyneuritis remains obscure except in those cases due to lead, mercury, or other noxious agents and in those following specific infectious or toxic diseases, such as diphtheria or certain types of streptococcal infection. In practically every case reported in the literature a general infectious process preceded the development of neurologic symptoms. In some patients the signs of infection had disappeared before the neurologic symptoms developed. In

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others a local generalized infection could still be found on admission to the various clinics. In other words, a latent period could be demonstrated between the preceding infection and the development of the polyneuritis. The type of infection initiating this cycle has varied tremendously. Staphylococcal,[26] streptococcal,[17, 20] and *Hemophilus influenzae*[26] origins have been discussed by various authors. The disease has been shown to coincide with an infectious focus: angina, tonsillitis, furunculosis, dental caries,[10] and abscessed teeth. It has been shown to supervene on a general infectious disease: mumps, mumps complicated by orchitis, mastitis,[21] measles, scarlet fever,[12] influenza, and even syphilis.[16] The lesion has been shown to manifest itself in the absence of an infectious focus or general infectious disease. This latter situation may be a primary infection by a neurotropic virus.[8] Further evidence to point to a virus etiology of polyradiculoneuritis is the work of Garvey, Jones, and Warren,[27] who described the development of the Guillain-Barré syndrome in patients after a latent period had elapsed following treatment with artificial fever. One may presume that the initial infection, such as diphtheria, various infectious diseases, perianal abscess, botulism, osteomyelitis, and other preceding illness merely activate the neurotropic virus, if such it be, already present in the central nervous system. Such a pathogenesis is alluded to by Gilpin, Moersch, and Kernohan[11] who reported thirty-five cases of neuronitis. This point of view is also maintained by numerous other contributors in the field.[19, 22, 25, 28] The toxic etiology suggested by Heernu[29] is on the basis of resemblance to polyneuritis following diphtheria. Such a hypothesis for the etiology of polyneuritis is also favored by Aring.[2]

PATHOLOGIC ANATOMY

In spite of the assertion of Guillain and Barré, that no patient with this disease dies, such a view is no longer tenable and pathologic reports continue to appear in the literature. These are at least worthy of note. Biemond[26] believes the disease is one due to an infectious agent which affects primarily the meningeal space from where the infection extends to the nervous parenchyma. Bassoe's[30] anatomical findings show that the pure syndrome presents a picture of meningoradiculoneuritis. Where the spinal cord is involved, the picture is that of meningoradiculoneuritis. However, such an anatomical picture represents a case of myelitis. The question, therefore, arises as to whether these cases should not be excluded from our consideration. De Morsier and Steinmann[7] believe the malady should be divided into two anatomical forms which differ in nothing but the evolution. Both are characterized by affection of the spinal nerve roots, sometimes extending to various cranial nerves. Facial paralysis is frequent and precocious. The fatal evolution is usually due to the involvement of the respiratory nerves. They observed one such case. The pathologico-anatomic picture found at autopsy coincided with

the description given by others:[4] There was intense perivascular lymphocytic infiltration of the nerves and roots, hemorrhagic foci, and marked increase of the nuclei of the sheaths of Schwann ("Schwannitis"), and complete integrity of the spinal marrow. In addition to these findings, patchy degeneration of the myelin and fragmentation of the axis cylinders of the peripheral nerves without evidence of inflammation have also been described.[11] Goolker[13] states that he noted glial reaction in the form of an increase in the number of oligodendroglia in one case which came to autopsy, but in this instance he could not have been dealing with polyneuritis alone. Soto and Dassen[22] report a third case in the literature where this syndrome was encountered in the course of a zona. The zona was concomitant with inflammation of the arachnoid. Operative exposure of the dura mater on their living patient revealed an inflammatory process of the arachnoid with the formation of cysts above. The cysts were cut and drained with subsequent rapid and complete clinical recovery of the patient.

CLINICAL CONSIDERATIONS

The greatest number of cases have been reported as occurring during July, August, and September.[23] According to Guillain,[5] a typical course of the disease can be described. The onset is abrupt with attacks of pain, paresthesia, or paralytic phenomena. There are motor disturbances first of lower extremities, later of trunk and upper extremities, leading sometimes to complete quadraplegia. Slight transitory facial palsy of the peripheral type is occasionally seen. The phrenic nerve is rarely involved. The paralysis is flaccid and associated with hypotonia. Hypertonia is only rarely encountered. Fibrillary twitchings are rarely observed. There is usually very little muscular atrophy. Ataxia is the general rule, the patient having a pseudotabetic appearance. Main losses are of tendon and periosteal reflexes. Idiomuscular contractility is preserved or exaggerated. Transitory changes of deep sensibility have been observed and described.

THE SPINAL FLUID FINDINGS AS A BASIS OF DIAGNOSIS

Lumbar puncture should be done and repeated when polyneuritis is suspected. The spinal fluid is characteristically clear. Xanthochromia has been observed only rarely. Hyperalbuminosis is constant. The Pandy test for globulin is positive. The cell count is practically always normal. The spinal fluid serology is negative. Albuminocytologic dissociation must be absolutely present before a diagnosis of Guillain-Barré syndrome, and, therefore, polyneuritis, may be made, according to Stone and Aldrich.[23] In a report of two cases they showed that more than one lumbar puncture may be necessary to uncover hyperalbuminosis with an acellular response since this may occur late in the disease. However, it must be remembered that an increased albumin is present in the

cerebrospinal fluid at some time during the course of almost any central nervous system disease.

PROGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of polyneuritis carries a good prognosis. Estimates of the mortality rate vary from 0 per cent by Guillain and Barré[31] to 14 per cent by American workers.[11] It is imperative, therefore, that a correct diagnosis be ascertained. Albuminocytologic dissociation is supposedly the most constant and characteristic feature of the syndrome. It may be found also in compression of the spinal cord and in Pott's disease,[5] but these are relatively easy to differentiate from the polyneuritis.[5] However, albuminocytologic dissociation is found also in late poliomyelitis, toxic neuritis, toxic and virus encephalitis, and tumors of the central nervous system.

THERAPY

It is practically impossible to evaluate properly the efficacy of any therapeutic measure in polyneuritis because of the tendency for spontaneous recovery in the average case. Numerous therapeutic measures have been reported in the literature. DeMello[6] used vitamin B_1 in his patient who was a 50-year-old male. Guillain[5] recommends an intravenous infusion of sodium salicylate, 1 to 2 Gm.,[18] in serum with 10 per cent dextrose. He also suggests intravenous or intramuscular quinine, methanamine, or colloidal silver. Rubs with colloidal silver are said to be of value. Ionized iodine or calcium given by the transcerebromedullary route, warm baths, and irradiation are recommended on an empirical basis. Plügge[32] used physiotherapy and electrical stimulation with good results in his patient. Aring[2] suggests that the Kenny treatment be given further trial. Removal of foci of infection is said to be of value in the immediate course of the disease.[10, 13, 20, 22]

FATAL CASE OF POLYNEURITIS OF UNKNOWN ETIOLOGY

S. Z., a single, white female 19 years of age, was admitted to the hospital Jan. 15, 1941. Respirations ceased Jan. 27, 1941.

Illness at Time of Admission to Hospital.—Five days prior to admission the patient noted the onset of pain in the lower back, dull and aching in character, but not radiating. One day later she complained of gradually ascending numbness in the hands and feet. The numbness gradually ascended. She then complained of weakness in the legs, and it was observed that the lower extremities were paralyzed and that the upper extremities were fast becoming paralyzed. On Jan. 15, 1941, dyspnea and dysphagia were first observed. This was followed by a feeling of slight numbness on the left side of the face, stiffness of the neck, and much muscle tenderness. The patient told of "infection" of the great toe two months before the onset of the illness and had complained of slight coryza one to two days before the illness. There had been little vomiting.

Physical Examination.—Temperature, 99.2° F.; pulse, 96; respiration, 24. The neck was rigid and painful. Otherwise the routine physical examination was negative.

Neurologic Examination.—Hyperesthesia of the third, fourth, and fifth sacral dermatomes was present. There was loss of vibratory sensation up to the iliac crests and at the wrists with proprioception lost in the left hand and left foot but preserved in the extremities on the right. There was generalized muscular tenderness and complete flaccid paralysis of both lower extremities. Extreme weakness of the back muscles as well as weakness of the upper extremities was noted. Slight plantar response was noted on the left with no response on the right. Kernig and Lasèque's signs were positive.

Laboratory Determination.—Blood Kahn was negative. Urine showed a few white cells but was otherwise negative. A complete blood count revealed a hemoglobin of 80 per cent (Sahli); red blood count, 4,100,000 per cubic millimeter; white blood count, 14,800 per cubic millimeter, of which 81 per cent were neutrophiles, 17 per cent lymphocytes, and 2 per cent monocytes. The red blood cells and platelets were morphologically normal. An initial lumbar puncture revealed a spinal fluid pressure of 60 mm. of water. The fluid was clear and colorless. No cells were observed. The gold sol was read at 1144433221. The mastic sol was read at 234432. Globulin by Pandy's test was 4 plus. Total protein was 400 mg. per cent. A repeat lumbar puncture revealed a pressure of 150 mm. of water. This fluid was xanthochromic with pellicle formation observed. No cells were seen. Globulin by Pandy's test was 4 plus. Gold sol was read at 4444443321. Mastic sol was 234443. Total protein was noted to be 1,333 mg. per cent.

Course in the Hospital.—The vital signs remained normal until the eleventh hospital day, when the temperature rose to 101° F., then suddenly fell to normal. By the thirteenth hospital day the temperature had risen to 106.4° F. The pulse rate was elevated in proportion to the fever. Codeine phosphate was administered for the pain in the back. On the third hospital day dyspnea and irregular respirations had been observed. These were of such severity that the patient required the use of a Drinker respirator. She was removed the following afternoon. Hypalgesia of the left side of the face and dysphagia had been observed but had disappeared. On the third hospital day the paralysis of the arms was definite. On the fifth hospital day respiratory distress again occurred, requiring the use of the Drinker respirator. On the eleventh hospital day there was marked dysphagia. The pharyngeal reflex was going. She required the Drinker respirator most of the time. On the twelfth hospital day she was unable to swallow and had to be fed by tube. On the thirteenth hospital day sulfapyridine was given by tube. Dysphonia was extreme. The patient was disoriented and irrational. She expired Jan. 27, 1941. An autopsy limited to the central nervous system was performed that day.

Pathological Findings.—The positive anatomical changes observed at autopsy were as follows: The brain was edematous and congested; the leptomeninges were delicate; the basal vessels were soft; sections showed marked hyperemia of the cortex and subcortical gray masses; there was hyperemia of the brain stem; and sections through the various levels of the dorsolumbar cord showed some hyperemia of the gray matter which at times was poorly demarcated from the whole substance.

Histologic study of the spinal cord, nerve roots, and the brain failed to show any signs of pathology other than the terminal hyperemia and occasional small hemorrhages in the cord.

The course and pathologic findings in this case are suggestive of ascending paralysis of the Landry type. However, the final diagnosis on the clinical record was Guillain-Barré syndrome.

SUMMARIZATION OF CLINICAL CASES

Seventeen patients under 20 years of age whose findings conform entirely or in part to the original description of polyneuritis of unknown etiology have been grouped in Tables I, II, and IIA.

TABLE I

Case Number	*333950*	*473963*	*350864*	*313048*	*420170*	*362172*
PATIENT	V. M. B.	S. Z.	N. L.	J. L.	D. C.	R. D.
AGE	8 yr.	19 yr.	2 yr.	16 yr.	4 yr.	17 yr.
SEX	Female	Female	Male	Male	Male	Male
MONTH OF OCCURRENCE	March	January	November	November	March	June
PRECEDING ILLNESS	None	Slight coryza	Pertussis	None	Acrodynia	None
LATENT PERIOD	None	1 to 2 days	5 months	None	4 months	None
MOTOR DISTURBANCES	Dysphonia, dysphagia, and weakness of extremities	Weakness, dysphonia, dysphagia, respiratory distress, flaccid quadriplegia	Flaccid paralysis of lower extremities	Paresis, left leg	Flaccid quadraplegia	Dysphonia and flaccid quadraplegia
TENDON JERKS	Decreased	Absent	Absent	Absent	Absent	Absent
PARESTHESIAS	None	Pain and numbness	None	Pain along distribution of D 11 and D 12	None	Numbness of fingers and feet
PSYCHE	Clear	Clear	Clear	Clear	Clear	Clear
MUSCLE TENDERNESS	None	Extreme	None	None	None	None
ELECTRICAL REACTIONS	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
SPINAL FLUID (TOTAL PROTEIN)	25 mg. %	1st, 4 mg. % 2nd, 1,333 mg. %	Not done	250 mg. %	222 mg. %	360 mg. %
PANDY GLOBULIN	Negative	1st, ++++ 2nd, ++++	+	++++	++++	++++
TEMPERATURE	Normal	99.2° F.	Normal	Normal	Normal	Normal
CELL COUNT	0	1st, 0; 2nd, 0	5/c. mm.	26L.*/c.mm.	10/c.mm.	1L./c.mm.
COURSE	Gradual improvement	Death on thirteenth hospital day	Descending recovery	Improvement after third week	Gradual improvement	Rapid improvement
RESIDUAL NEUROLOGIC FINDINGS	None	Autopsy	None	None	None	None

Case Number	*441646*	*460877*	*460059*	*268315*	*440323*	*422837*
PATIENT			R. F.	K. T.	J. W.	H. E. N.

Case Number	*441646*	*460877*	*460059*	*268315*	*440323*	*422837*
PATIENT	J. N. S.	A. O.	R. E.	K. T.	J. W.	H. E. N.
AGE	17 yr.	8 yr.	6 yr.	9 yr.	5 yr.	3 yr.
SEX	Male	Male	Male	Male	Female	Male
MONTH OF OCCURRENCE	March	December	March	July	May	September
PRECEDING ILNESS	U. R. I.	Convulsive disorder	Carious teeth	Otitis media	Acrodynia	U. R. I.
LATENT PERIOD	4 weeks	5 months	6 weeks	3 weeks	None	2 days
MOTOR DISTURBANCES	Flaccid lower extremities, hypotonia left arm, bilateral wrist drop	General weakness, right facial paralysis	Weakness of legs	Weakness both legs	Weakness of extremities	General hypotonia
TENDON JERKS	Sluggish; absent KK and AK	Absent right AK, positive bilateral Kernig and Brudzinski signs, hypoactive	Absent	Absent	Hypoactive	Absent
PARESTHESIAS	Numbness of hands and feet	None	Feeling of heaviness of feet	Pain in both calves	None	Pain in arms
PSYCHE	Clear	Clear	Clear	Clear	Clear	Clear
MUSCLE TENDERNESS	Extreme	None	None	Marked	None	Marked in calves and arms
ELECTRICAL REACTIONS	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
SPINAL FLUID (TOTAL PROTEIN)	1st, 333 mg. % 2nd, 200 mg. % 3rd, 100 mg. %	268 mg. %	364 mg. %	125 mg. %	Lumbar puncture not performed	Not done
PANDY GLOBULIN	1st, ++++ 2nd, ++++ 3rd, ++++	++++	++++	++++		+
CELL COUNT	1st, 1L./c.mm. 2nd, 4L./c.mm. 3rd, 2L./c.mm.	3/c.mm.	0	8/c.mm.		5L./c.mm.
TEMPERATURE	Normal	Normal	Normal	Normal	Normal	99.6° F.
COURSE	Slow improvement	Slow improvement	Gradual spread of weakness to upper extremities, then arrest of symptoms	Gradual improvement	Gradual improvement	Gradual improvement
RESIDUAL NEUROLOGIC FINDINGS	None	Convulsive disorder (?etiology)	Bilateral varus deformity of forefoot	None	None	Flaccid paralysis lower extremities

*L., Lymphocytes.

TABLE I—CONT'D

Case Number	*423649*	*424003*	*424048*	*374001*	*507460*	
PATIENT	C. J. A.	P. R. B.	J. P.	E. C.	S. S. S.	
AGE	2½ yr.	10 yr.	15 yr.	6 yr.	4½ yr.	
SEX	Male	Male	Female	Male	Female	
MONTH OF OCCURRENCE	April	May	May	December	June	
PRECEDING ILLNESS	U. R. I.	Measles	Chronic sinusitis	Scabies	Sore throat	
LATENT PERIOD	5 weeks	3 weeks	Unknown	9 weeks	1 week	
MOTOR DISTURBANCES	Paresis, lower legs	Flaccid paralysis, lower extremities	Dysphonia, generalized hypotonia	Weakness of all extremities	Weakness of back and legs	
TENDON JERKS	Absent	Absent	Absent	Absent	Absent	
PARESTHESIAS	None	Headache, back pain	Numbness and tingling in hands and feet	Pain in legs and arms	Headache	
PSYCHE	Clear	Clear	Clear	Clear	Clear	
MUSCLE TENDERNESS	None	None	None	Marked in calves and forearms	Marked	
ELECTRICAL REACTIONS	Not tested	Not tested	Not tested	Reaction of degeneration	Not tested	
SPINAL FLUID (TOTAL PROTEIN)	Normal	Not done	500 mg. %	++++	1st 264 mg. %	2nd 128 mg. %
PANDY GLOBULIN		+	+	++	++++	++++
CELL COUNT		9L./c.mm.	8L./c.mm.	3L./c.mm.	4L./c.mm.	4L./c.mm.
TEMPERATURE	Normal	Normal	Normal	Normal	Normal	
COURSE	Rapid improvement	Very slow improvement	Marked improvement	Very slow, slight improvement	Rapid improvement	
RESIDUAL NEUROLOGIC FINDINGS	None	Transverse myelitis at segment 12 D	None	Flaccid paralysis of lower tremities	Weakness of arms and legs; absent tendon reflexes	

TABLE II

SUMMARY OF SEVENTEEN CASES

		THEORETICAL IDEAL CASE ACCORDING TO THE LITERATURE
AGE	Average age, 9 yr.	20-50 yr.
SEX	12 males; 5 females	Equal distribution
MONTH OF OCCURRENCE	Jan., 1; Feb., 0; March, 4; April, 1; May, 3; June, 2; July, 1; Aug., 0; Sept., 1; Oct., 0; Nov., 2; Dec., 2	July, August, or September
PRECEDING ILLNESS	U.R.I., 7; none, 3; acrodynia, 2; pertussis, 1; measles, 1; scabies; convulsive disorder, 1; dental caries, 1	Present
LATENT PERIOD	0 days, 4; 1 to 7 days, 3; 8 to 31 days, 3; 32+ days, 6; unknown, 1	Present
MOTOR DISTURBANCES	Weakness of lower extremities progressing to flaccid paralysis with tendency toward ascending involvement—all cases; dysphonia, 4; dysphagia, 2	Paralytic phenomena first of lower extremities, later of trunk and upper extremities
TENDON JERKS	Absent, 15; decreased, 2	Absent
PARESTHESIAS	Present, 11; none, 6	Present
PSYCHE	Clear in all cases	Clear
MUSCLE TENDERNESS	None, 11; present, 6	Present
ELECTRICAL REACTIONS	Not tested, 16; reaction of degeneration, 1	Little or no change
SPINAL FLUID (TOTAL PROTEIN)	Average, 329 mg. %	Elevated
PANDY GLOBULIN	++++, 9; ++, 1; +, 4; 0, 2; ?, 1	Positive
CELL COUNT	Average 5L./c.mm.	Normal
TEMPERATURE	Normal in all cases	Normal
COURSE	Improvement, 15; arrest of symptoms, 1; death, 1	Disorders may increase but patient finally recovers
RESIDUAL NEUROLOGIC FINDINGS	None, 11; weakness, 1; paralysis, 3; orthopedic deformity, 1; death with autopsy, 1	None

DISCUSSION

An analysis of the accumulated data compared with the theoretical ideal case reveals the following information: The average age of our patients was 9 years in this selected group, while the usual age range for all patients reported in the literature is from 20 to 50 years. Males outnumbered females three to one, although the disease is supposed to be equally distributed in the two sexes. Although the months of greatest incidence are reported to be July, August, and September,[25] the onset in only two of our patients occurred during this summer period. In this series the most frequent months of onset were those of March, April, June, November, and December. In every patient but one a history of preceding illness was obtained. However, the latent period between the first illness and the onset of the polyneuritis varied from two days to

TABLE IIA

	IDEAL CASE ACCORDING TO FOREGOING FINDINGS	POLYNEURITIS FOLLOWING SULFATHIAZOLE	POSTDIPHTHERITIC POLYNEURITIS
		489965	133692
PATIENT		P. C. R.	M. K.
AGE	Average age, 9 yr.	16 yr.	15 yr.
SEX	Usually male	Male	Female
MONTH OF OCCURRENCE	March, April, June, or December	September	February
PRECEDING ILLNESS	Present	Mastoiditis treated with sulfathiazole	Diphtheria
LATENT PERIOD	Present but apparently unrelated	12 days	2 months
MOTOR DISTURBANCES	Paralytic phenomena first of lower extremities, later of trunk and upper extremities	Extreme weakness and ataxia	Diminished power in left leg
TENDON JERKS	Absent or decreased	Decreased	Absent
PARESTHESIAS	Usually present	Numbness in lower extremities and photophobia	None
PSYCHE	Clear	Clear	Clear
MUSCLE TENDERNESS	Usually absent	None	None
ELECTRICAL REACTIONS	No data	Not tested	Not tested
SPINAL FLUID (TOTAL PROTEIN)	Elevated	200 mg. %	46 mg. %
PANDY GLOBULIN	Positive	++++	+
CELL COUNT	Normal	62L./c.mm.	2L./c.mm.
TEMPERATURE	Normal	Normal	Normal
COURSE	Improvement is the general rule but a fatal termination is possible	Rapid improvement	Continued improvement
RESIDUAL NEUROLOGIC FINDINGS	Usually none but continued flaccid paralysis is possible	None	Diminished tendon reflexes

five months, thus casting great doubt on the relationship between the two. In other respects the polyneuritis included dysphonia and dysphagia as well as paralytic phenomena of the extremities. Moreover, muscle tenderness was not encountered as frequently as reports for adult cases would indicate. In all patients in whom a lumbar puncture was performed, albuminocytologic dissociation was found. The average total protein determination was reported as 329 mg. per cent with an average cell count of 5 per cubic millimeter, all lymphocytes. This corresponds with the experience of the literature. In eleven patients ob-

served in this series, there was either complete recovery or only slight residual neurologic findings. However, there was residual flaccid paralysis in three individuals and a persistent residual orthopedic deformity in one individual. One patient had persistent muscular weakness and areflexia. Another patient, whose case has been presented in greater detail, expired on the thirteenth day.

One case of polyneuritis following administration of sulfathiazole and one case of postdiphtheritic polyneuritis have been summarized. Comparison of these cases with those of unknown etiology reveals no significant difference.

In the present state of our knowledge, therefore, the use of the appellation Guillain-Barré syndrome is not warranted for these cases. They are cases of polyneuritis of unknown etiology and should thus be known until such time when they can be separated on an etiologic or pathologic basis.

CONCLUSIONS

1. In a series of cases of polyneuritis of unknown etiology in patients under 20 years of age it was found that this illness in the pediatric age group follows essentially the same pattern as for the older age groups with the following differences:

a. Males outnumbered females three to one.

b. The average age of these patients was 9 years.

c. The usual time of onset was during cool weather.

d. A history of preceding illness was obtained in all cases, but the varied periods of time elapsing between the previous illness and the polyneuritis made the causal relationship between the two very doubtful.

e. Dysphonia and dysphagia were observed in addition to paralytic phenomena of the extremities.

f. Muscle tenderness was usually absent.

g. The disease is not as benign as the literature would lead one to believe.

2. Polyneuritis of unknown etiology follows the same course as polyneuritis of known etiology.

3. The use of a proper name such as Guillain-Barré syndrome is not justified for polyneuritis of unknown etiology.

4. A fatal case is presented. Autopsy findings disclosed no characteristic changes.

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THE WEIGHT OF NEGRO INFANTS

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ACCORDING to reports in the literature, the Negro infant in the United States is smaller at birth than the white infant[1, 2, 3] and growth during the first year of life is slower.[2, 4] It is not clear from the available data whether these differences are due to innate or to environmental influences, since observations on Negro children have been limited to dispensary material.

This study was made on a group of Negro infants seen in private practice and supervised from early life by one of us (T. W. P.). Six hundred seventy-nine observations were made on 114 infants. About 40 per cent were breast fed for the first three to four months of life, the remainder receiving evaporated milk dilutions with added carbohydrate (cane sugar, Karo, or dextrimaltose). Similar mixtures were given to infants who were weaned before 6 months of age. About 90 per cent of infants received from 10 to 15 drops of percomorph oil daily at 3 to 4 weeks and the remainder received cod-liver oil in increasing doses up to 3 teaspoons a day at 3 months. Orange juice was given at the same time in increasing amounts up to 3 ounces at 3 months. Cereal was introduced at from 2½ to 3 months, vegetable and fruit at from 4½ to 5 months. Potato and egg yolk were added at 6 months and meat at about 11 months.

TABLE I

THE WEIGHT OF NEGRO INFANTS DURING THE FIRST YEAR OF LIFE

AGE RANGE (WK.)	MALES				FEMALES			
	NUMBER OF CASES	MEAN AGE (WK.)	MEAN WEIGHT (KG.)	STANDARD DEVIATION (KG.)	NUMBER OF CASES	MEAN AGE (WK.)	MEAN WEIGHT (KG.)	STANDARD DEVIATION (KG.)
4 to 7	40	5.6	4.36	.330	39	5.8	4.05	.289
8 to 15	54	11.7	5.72	.370	57	11.7	5.18	.368
16 to 23	46	21.2	7.32	.308	48	20.3	6.68	.412
24 to 31	46	29.0	8.24	.426	55	28.6	7.61	.460
32 to 39	48	37.2	9.08	.532	45	36.9	8.86	.570
40 to 47	48	43.8	9.73	.496	58	43.5	9.36	.672
48 to 55	45	52.0	10.50	.471	50	52.0	10.03	.689

Means and standard deviations for the weights of Negro infants by certain subdivisions of age under 1 year are shown in Table I. In Fig. 1 the data are compared with those obtained from a group of white infants supervised from early life at the Fifth Avenue Hospital.[5]

From the Children's Medical Service of Bellevue Hospital and the Department of Pediatrics, New York University.

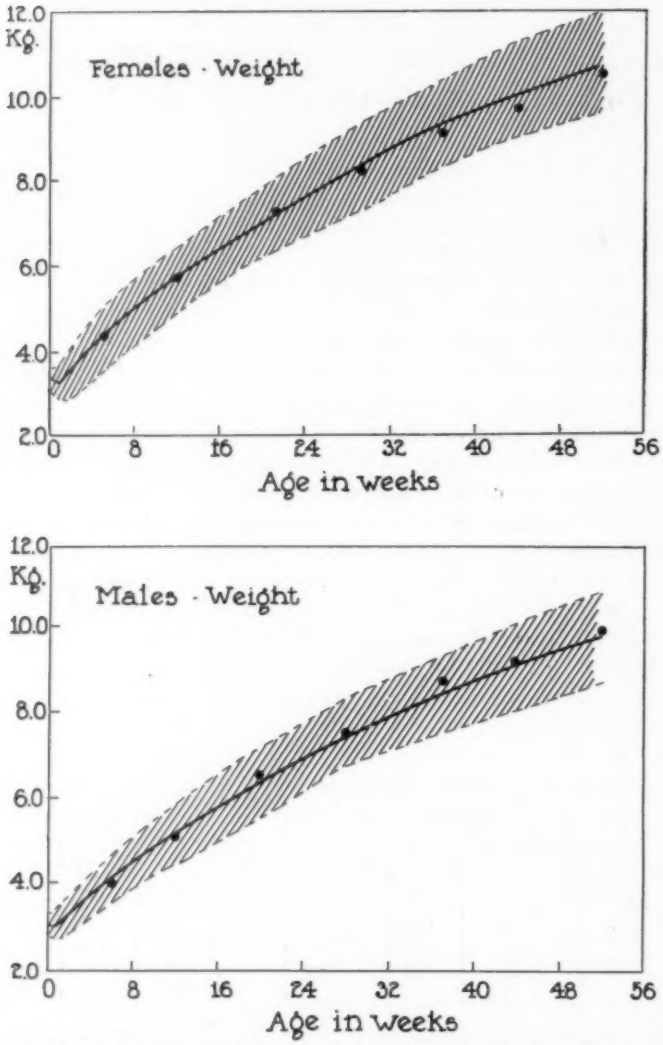

Fig. 1.—Comparison of the weight of Negro and white infants. The continuous lines represent the average weight curves for white infants. The cross-hatched areas included between the dotted lines represent 1 standard deviation above and 1 standard deviation below the mean. The dots represent average weights for groups of Negro infants by certain subdivisions of age.

There is no significant difference in the weight gain of white and Negro infants during the first year of life. It seems likely that the slower growth observed in earlier studies was due to differences in socioeconomic status rather than to differences in the nature of the germ plasm. Given the opportunity of proper medical supervision, Negro infants from moderate income families grow as well as white infants.

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INFLUENZAL MENINGITIS

A Review of Fifteen Cases With Two Unusual Cases Reported in Detail

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PRIOR to the use of the sulfonamides, the diagnosis of *Hemophilus influenzae* meningitis carried with it a dire prognosis. In 1922 Rivers[1] stated that the mortality rate varied from 90 to 100 per cent, depending upon the age of the patient. The younger the child, the higher the mortality rate. Since the advent of sulfonamide therapy, there has been a marked decrease in the mortality rate. Neal, Appelbaum, and Jackson,[2] in 1940, reported on twenty-nine patients, with fourteen recoveries, treated with sulfapyridine, sodium sulfapyridine and anti-influenzal horse serum. In five of the patients who recovered, drug therapy alone was used. Patterson and Crumpton,[3] in 1941, reported on a patient with *H. influenzae* meningitis treated successfully with sulfathiazole. Sako, Stewart, and Fleet,[4] in 1942, in a preliminary report on the treatment of seven patients with sulfadiazine, reported only two deaths. Two of these patients were given anti-influenzal rabbit serum in addition to drug therapy. The general trend in therapy is emphasized in a ten-year survey at the Los Angeles County Hospital from 1931 to 1941 made by Knouf, Mitchell, and Hamilton,[5] who reported on a total of sixty-three cases. These cases were separated into four groups. In Groups 1, 2, and 3, respectively, the patients were treated symptomatically with Fothergill's anti-influenzal horse serum and with sulfanilamide and Fothergill's serum. Of the fifty-one patients treated in these three groups only one survived. In Group 4, consisting of twelve patients treated with sulfapyridine and Fothergill's serum, there were ten recoveries. The authors stated that since thirty-two other patients who received Fothergill's serum alone had all succumbed, the good results obtained in the patients in Group 4 were apparently due to the sulfapyridine and not to the serum.

In 1939 Alexander[6] made available for therapeutic purposes a specific anti-influenzal rabbit serum. In a summary of fifty cases in patients treated with sulfanilamide and rabbit serum by Alexander, Ellis, and Leidy[7] over a four-year period from 1938 to 1941, there were only thirteen fatalities, or a mortality rate of 26 per cent. Scully and Menten[8] reported a mortality rate of 44 per cent in nine patients treated with type-specific rabbit serum and sulfapyridine.

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We wish to report fifteen cases of *H. influenzae* meningitis in patients treated on the pediatric wards of the Kings County Hospital (Long Island College of Medicine Division) and the Long Island College Hospital during the six-year period from 1938 to 1943. Apart from the statistical value in adding this series of cases to the literature, we feel that several distinctive points of interest stem from this material. These patients have all been treated similarly and establish the value of a planned routine.

Two of the cases are reported in detail. The first one emphasizes the necessity for prolonged drug therapy in one patient and the other presents an interesting drug reaction during the course of therapy in another patient.

In this series of fifteen patients, there were nine recoveries, one of which was complicated by hydrocephalus. The mortality rate for the whole group was 33 per cent. Of the six deaths, two occurred in pa-

TABLE I

CASES ARRANGED CHRONOLOGICALLY TO DEMONSTRATE EVOLUTION OF THERAPY

	NAME	SEX	AGE	DATE	ILL AT HOME	STAY AT HOSPITAL	TREATMENT	OUTCOME
1.	C. M.	F.	10 mo.	1938	1 wk.	12 days	Sulfanilamide Sulfapyridine Fothergill's serum	Died
2.	M. C.	F.	14 mo.	1938	2 wk.	5 wk.	Sulfanilamide Sulfapyridine Fothergill's serum	Died
3.	E. D.	M.	7 mo.	1940	4 days	7 hr.	Sulfapyridine	Died
4.	A. W.	F.	4 mo.	1940	10 days	37 days	Sulfapyridine Horse serum*	Died
5.	S. B.	F.	5 yr.	1941	3 days	35 days	Sulfapyridine Horse serum	Recovered
6.	W. S.	M.	6 yr.	1941	2 days	6 wk.	Sulfapyridine Horse serum	Recovered
7.	E. R.	F.	4 yr.	1941	1 day	63 days	Sulfapyridine Sulfadiazine Rabbit serum†	Recovered
8.	R. S.	M.	7 yr.	1942	1 day	29 days	Sulfapyridine Sulfadiazine Rabbit serum	Recovered
9.	G. S.	M.	2½ yr.	1942	4 days	14 hr.	Sulfapyridine	Died
10.	D. N.	F.	3 yr.	1942	2 days	24 days	Sulfathiazole Sulfadiazine Rabbit serum	Recovered
11.	J. R.	F.	9 mo.	1942	4 wk.	1 mo.	Sulfadiazine Sulfapyridine Rabbit serum	Recovered (internal hydrocephalus)
12.	T. G.	M.	6 mo.	1942	2 wk.	17 days	Sulfathiazole Sulfadiazine Rabbit serum	Died
13.	B. F.	F.	2 yr.	1942	2 days	40 days	Sulfapyridine Rabbit serum	Recovered
14.	V. M.	M.	23 mo.	1942	12 hr.	1 mo.	Sulfapyridine Rabbit serum	Recovered
15.	J. R.	M.	4 yr.	1943	24 hr.	24 days	Sulfapyridine Rabbit serum	Recovered

*Horse serum supplied by New York City Health Department.
†Rabbit serum prepared by E. R. Squibb & Sons.

tients who were in the hospital for but seven and fourteen hours, respectively. As is commonly observed, the deaths were almost entirely in the group under 2 years of age. Eight of the patients in this series of fifteen received combinations of chemotherapy and type-specific anti-influenzal rabbit serum (Alexander[6]) and seven of the eight recovered.

CASE 1 (No. 7 in Table I).—E. R., a 4-year-old white girl, was admitted to the Kings County Hospital Nov. 30, 1941, because of headache, fever, and drowsiness of twenty-four hours' duration.

The child had appeared well until the day before admission, when she complained of a headache. At the same time she became drowsy and lost interest in her playthings. She became flushed, feverish, and progressively more drowsy. Hospitalization was advised by the attending physician.

The family history was not unusual, and the past history was noncontributory.

Physical examination upon admission disclosed a well-developed and well-nourished girl, gravely ill, and comatose. The rectal temperature was 105° F. The pulse was 140, and the respirations were rapid and shallow. Other than a moderate degree of upper respiratory infection with catarrhal otitis media, the principal findings were limited to the central nervous system. Neck rigidity was marked and the Kernig and Brudzinski reflexes were positive.

A presumptive diagnosis of meningitis was made and a lumbar puncture was performed. A cloudy fluid under 12 mm. mercury pressure was obtained. The cell count was 1,970, predominantly polymorphonuclear leucocytes. The protein content was 319 mg. per cent; chlorides, 740 mg. per cent. The spinal fluid sugar was too low for quantitative estimation. The Gram-stained smear demonstrated long and short chained cocci of questionable staining characteristics. The red cell count was 5,900,000, hemoglobin 14 Gm. The white blood cell count was 6,800 with 72 per cent polymorphonuclears. A urine analysis was normal.

A tentative diagnosis of streptococcus meningitis was made, for which therapy was instituted. This consisted of 20 c.c. of neoprontosil given intravenously, as well as 50 gr. of sulfanilamide by mouth. A similar amount of neoprontosil was given twelve hours later, and sulfanilamide was continued in 15 gr. doses every three hours for the first day. At this time, reports of the blood and spinal fluid cultures taken on admission identified *H. influenzae* group b as the causative organism.

In view of this evidence, the neoprontosil and sulfanilamide were discontinued. Sodium sulfapyridine, 30 gr. of a 5 per cent solution, was given intravenously and 10 c.c. of horse anti-influenzal serum were given intramuscularly. Sulfapyridine was continued orally in 15 gr. doses every four hours. During the next thirty-eight days the child received 230 Gm. by mouth, by vein, and by rectum. Blood titers of the drug during this period ranged from 4.7 to 8.5 mg. per cent and spinal fluid titers, from 3.6 to 7.9 mg. per cent. Repeated small transfusions and intravenous fluids were administered as supportive measures. During this forty-day period of sulfapyridine therapy, the child appeared fairly well, with occasional spells of irritability and drowsiness. After a drop in temperature from 105° F. on admission to 99° F. twenty-four hours later, the temperature course was irregular and hovered between 100 and 102° F., with occasional rises to 104° F. Seven spinal fluid cultures during the first twenty-seven days were positive for *H. influenzae*. After the initial positive blood culture, all subsequent cultures were sterile. On the twenty-eighth day a single sterile spinal fluid culture was reported, but five days later, on the thirty-second hospital day, the culture was again reported positive.

On the fortieth day, because of persistent elevated temperature, positive spinal fluid cultures, and recurrent periods of drowsiness and irritability, the therapy was changed. Sulfapyridine was discontinued and sulfadiazine was started by mouth

in 15 gr. doses every four hours. In all, the child received a total of 47.5 Gm. of sulfadiazine, administered during the fortieth to forty-eighth days, inclusively. Drug titers in the blood reached 14.6 mg. per cent, while titers in the spinal fluid reached 10.5 mg. per cent.

At the time of the initial dose of sulfadiazine, the patient was given 10 c.c. of rabbit anti-influenzal serum (50 mg. of precipitable antibody nitrogen) intraspinally and 10 c.c. intravenously. The latter was diluted with 200 c.c. of saline, to which had been added 1 c.c. of 1:1000 adrenalin.

Two days before sulfadiazine was started, while the patient was still receiving sulfapyridine, the white blood cell count was 6,600 with 30 per cent polymorphonuclears, 68 per cent lymphocytes, and 2 per cent monocytes. Prior to this count, sixteen previous counts had been done. These ranged from 3,650 to 12,800, with a minimum of 61 per cent mature granulocytes. During the fortieth to forty-eighth days, while sulfadiazine was being administered, the white cell count fell progressively, so that on the forty-eighth day the total white count reached 2,600 with only a single mature granulocyte visible on the smear. At this time sulfadiazine was discontinued and an additional dose of 10 c.c. of rabbit serum was administered intravenously. Supportive blood transfusions were given as well as 60 c.c. of Pentnucleotide intramuscularly. On the fiftieth and fifty-first days no granulocytes were present on the blood smear, but on the fifty-third day, ten days after the withdrawal of sulfadiazine therapy, the white cell count reached 5,700, with 44 per cent mature forms of polymorphonuclears. At no time during this period of agranulocytosis did the patient present any evidence of a bleeding tendency. No petechiae or purpuric manifestations were noted. There was no gingival bleeding, and urine examinations failed to disclose red cells. The child was playful and her general condition was good.

On the forty-sixth day, one day before sulfadiazine was discontinued, a sterile spinal fluid culture was reported. For the next eleven days, during the period of agranulocytosis, no anti-influenzal serum was given. The temperature course was normal and the child was alert and friendly. On the fifty-seventh day another spinal fluid culture was reported as sterile.

On the sixty-third day the patient was discharged, having completely recovered from the influenzal meningitis and the complicating agranulocytosis.

Subsequent follow-up in the pediatric outpatient department one year later revealed a normal child who attended school successfully and who had no apparent evidence of sequelae from influenzal meningitis.

Case 2 (No. 13 in Table I).—B. F., a 2½-year-old white girl, was referred to the hospital by Dr. Lewis A. Koch. The child had been well until two days before admission, when she suddenly began to have nonprojectile vomiting and chills. Her temperature rose to 105° F. on the day of admission, followed by generalized convulsions.

On admission the child was conscious. There was evidence of an upper respiratory infection. The neck was stiff, and there was a questionable Kernig on the left side. The temperature was 103° F. and the pulse rapid.

The lumbar puncture done on entry revealed cloudy spinal fluid under increased pressure. There were 2,900 white cells per cubic millimeter, with 50 per cent polymorphonuclear and 50 per cent lymphocytes. The sugar content was 25 mg. per cent; protein, 60 mg. per cent; chlorides, 670 mg. per cent. Culture of the spinal fluid was positive for *H. influenzae* group b. A blood count showed 3,190,000 red cells, 10 Gm. of hemoglobin, and 19,000 white cells, with 37 per cent polymorphonuclear, 22 per cent lymphocytes, and 41 per cent monocytes. A urine analysis was normal. Cultures of the nose and throat showed hemolytic streptococci and *Streptococcus viridans* in large numbers.

The child was given 15 gr. of 5 per cent sodium sulfadiazine intravenously, followed by an infusion of 5 per cent glucose. After this single initial dose, the

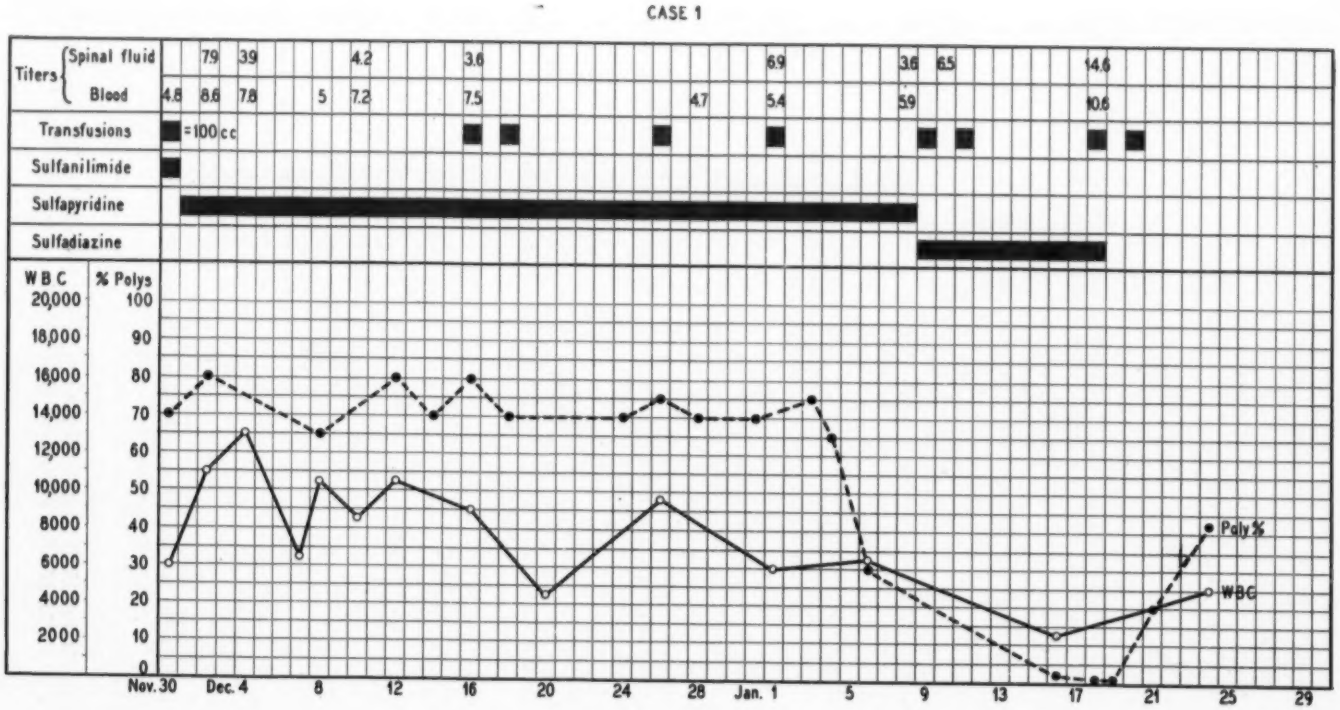
CASE 1
Titers
Spinal fluid
Blood
7.9
3.9
4.2
3.6
6.9
3.6
6.5
14.6
4.8
8.6
7.8
5
7.2
7.5
4.7
5.4
5.9
10.6
Transfusions
=100 cc
Sulfanilimide
Sulfapyridine
Sulfadiazine
WBC
% Polys
20,000
18,000
16,000
14,000
12,000
10,000
8000
6000
4000
2000
100
90
80
70
60
50
40
30
20
10
0
Poly %
WBC
Nov. 30
Dec. 4
8
12
16
20
24
28
Jan. 1
5
9
13
17
21
25
29

Fig. 1.

CASE 2

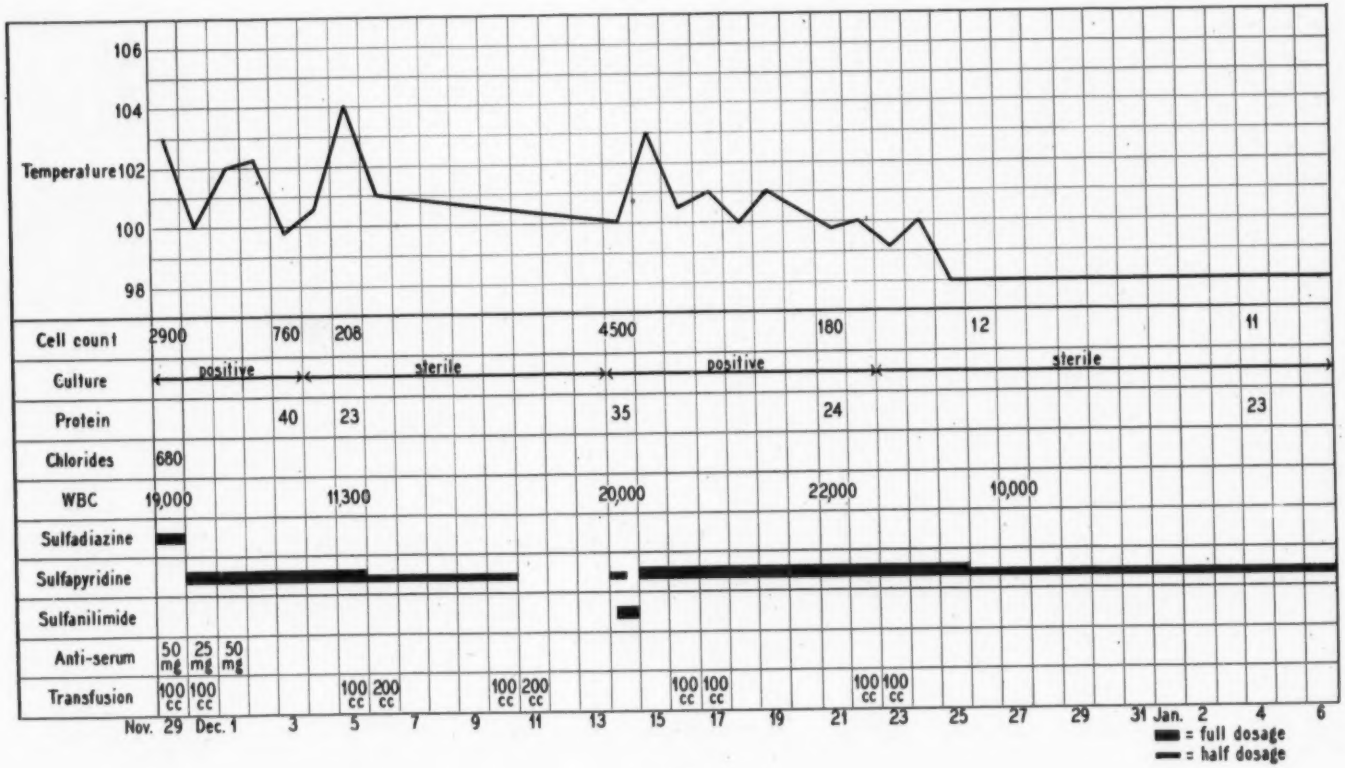
106
104
Temperature 102
100
98
Cell count
2900
760
208
4500
180
12
11
Culture
positive
sterile
positive
sterile
Protein
40
23
35
24
23
Chlorides
680
WBC
19,000
11,300
20,000
22,000
10,000
Sulfadiazine
Sulfapyridine
Sulfanilimide
Anti-serum
50 mg
25 mg
50 mg
Transfusion
100 cc
100 cc
100 cc
200 cc
100 cc
200 cc
100 cc
100 cc
100 cc
100 cc
Nov. 29
Dec. 1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
Jan. 2
4
6
= full dosage
= half dosage

Fig. 2.

drug was changed to sulfapyridine. Thirty grains of the drug were given intravenously and continued in doses of 11½ gr. every four hours. In addition, 10 c.c. of anti-influenzal rabbit serum diluted in 250 c.c. of saline, to which had been added ½ c.c. of 1:1000 adrenalin, were administered intravenously. Later the same day, the child received a transfusion of 100 c.c. of blood. The rabbit serum and the transfusion were repeated on the second hospital day. On the third and fourth days, the patient's serum gave a positive agglutination with the serum diluted 1:5 and 1:20, respectively.

The general condition of the child improved satisfactorily. Cultures of the spinal fluid on the first, third, and fifth days were positive for *H. influenzae*. On the seventh day the spinal fluid was sterile. The cell count had fallen to 208 per cubic millimeter, predominantly lymphocytes. The child appeared cheerful and alert, and all abnormal neurologic signs had disappeared. The dose of sulfapyridine was reduced to 7½ gr. every six hours. During the first ten days the patient received four blood transfusions of 100 c.c. each.

From the thirteenth to the sixteenth days the child received no chemotherapy. The temperature remained 99° F. On the sixteenth day the temperature rose to 103° F. and the child developed nuchal rigidity. The spinal fluid again appeared cloudy and contained 4,500 white cells, chiefly polymorphonuclears. The culture was again positive. A second course of chemotherapy was begun, the child receiving sulfapyridine in doses of 7½ gr. every four hours, and was continued until the twenty-ninth hospital day. On this drug the child's temperature subsided and the neurologic signs disappeared. She received four more transfusions of blood during the second course of chemotherapy. Repeated spinal taps showed steady improvement, until on the twenty-sixth day, ten days after sulfapyridine was resumed, the spinal fluid culture was again sterile. Subsequent cultures remained sterile. On the thirtieth day the drug was reduced to 3¾ gr. every four hours and was continued until the day of discharge on the fortieth day, despite the absence of all abnormal signs. For two weeks prior to discharge the temperature was normal and the child seemed cured. No exacerbations occurred after discharge.

DISCUSSION

Over the six-year period during which these cases were accumulated, a definite routine of therapy was evolved.

When the diagnosis of meningitis is considered tenable, the patient is immediately isolated. A lumbar puncture is performed and the spinal fluid examined by the intern. Part of the specimen is sent to the bacteriology laboratory. A third part of the spinal fluid is sent for chemical analysis. Venous blood is withdrawn for culture, typing, and cross-matching, and a continuous slow drip infusion of normal saline is started.

As soon as the diagnosis of *H. influenzae* meningitis is established by a Gram-stained smear, blood culture, spinal fluid culture, or a positive quellung reaction with type-specific anti-influenzal rabbit serum, the patients are started on intravenous injections of 5 per cent sodium sulfapyridine. The initial dose is from 2 to 3 Gm., depending upon the child's age and weight. When the patients are able to retain oral medication, sulfapyridine is given in periodic maintenance doses, calculated on the

basis of from 1.5 to 2 gr. per pound per twenty-four hours. Frequent blood drug titers and cultures are done on each patient.

Blood counts and urine analyses are done shortly after admission and repeated every third or fourth day. Daily urine examinations and blood counts are done in those patients where there is any evidence of drug toxicity.

Within twenty-four hours after admission, the patient receives from 10 to 15 c.c. of anti-influenzal rabbit serum (from 50 to 75 mg. of precipitable antibody nitrogen) after a negative intradermal skin test. The serum, diluted with normal saline or Ringer's solution, to which has been added 1:1000 adrenalin, is given intravenously.

Blood antibody titers are measured at variable intervals after the administration of the rabbit serum. This is done by performing the quellung test on *H. influenzae* organisms with the patient's serum diluted. A positive capsular swelling reaction with a dilution of 1:10 or more indicates adequate amounts of circulating antibodies. When the response is inadequate, or when the clinical course is unsatisfactory, an additional intravenous dose of rabbit serum is given as on admission.

Lumbar punctures are repeated as indicated. The number of taps are variable, depending on the response of the patient. A definite attempt is made to perform a minimum of punctures. Specimens obtained at each tap are examined by the intern, bacteriologically and chemically, including drug titers.

Whenever the patient has received adequate amounts of sulfapyridine with a poor response, the drug is changed. Sulfadiazine and sulfathiazole are used as alternates.

Part of the nonspecific supportive therapy employed is the use of frequent small blood transfusions. All patients receive frequent transfusions during the critical phase of their illness. As they improve, the use of transfusions is discontinued. In Case 2, reported above, the patient received ten transfusions for a total of more than 1,000 c.c. of blood. It is our opinion that frequent transfusions often helped to tide the gravely ill patients over the early part of their illness, thus permitting the effective use of chemotherapy and specific rabbit serum in aiding recovery of the patient.

The chemotherapy is gradually reduced as the clinical improvement warrants. Periodic blood sulfapyridine titers are done to check the blood levels.

After the blood and spinal fluid cultures become sterile and the clinical course of the patient is satisfactory, the chemotherapy is continued from two to three weeks. One experience with too early cessation of drug therapy led to exacerbation of the meningitis (Case 2). Final discharge came when the patient remained well after the discontinuance of the drug.

SUMMARY

1. A series of fifteen cases of *H. influenzae* meningitis is reported with nine recoveries.

2. Two cases are reported in detail—one in which the patient's condition was complicated by agranulocytosis and one in which the patient had a relapse after an apparent recovery, due to the lack of continued drug therapy.

3. A prepared plan of therapy including drug, rabbit serum, and blood transfusions has been outlined. The drug of choice in this series was sulfapyridine.

ADDENDUM

Since submitting this paper for publication, two more patients with influenzal meningitis, 10 and 14 months of age, have been treated with complete recovery.

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STUDY OF THE SERUM LIPIDS IN THE CELIAC SYNDROME

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STUDIES concerning the problem of the celiac syndrome, which has interested investigators and clinicians in the field of pediatrics for more than one-half a century, seem to divide themselves into three periods. In the first, the clinical symptoms and the pathology of the disease were considered, while in the second, metabolic studies were undertaken. In the third period the various features have been integrated so as to make it possible to define a clinical picture in which the pancreas as well as congenital anomalies and vitamin deficiencies may all play a role to produce a characteristic syndrome. Special credit must be given to Andersen[1] for clarification of the problem in this country. Since her report in 1938 the classical concept of "celiac disease" has been broadened to include the intimate relation of the pathologic changes in the pancreas to this condition, and as a result the new concept of the "celiac syndrome" has been accepted. Cystic fibrosis of the pancreas with or without the accompanying pulmonary pathology is the most characteristic feature of this syndrome. Because of this different approach to the problem, much has been achieved in the understanding of the pathology of the disease; however, the explanation of the faulty metabolism in these patients is not yet clear. Even with a nonfunctioning pancreas and the consequent absence of the pancreatic enzymes in the intestinal tract, the steatorrhea in this condition is composed of split fat (fatty acids and soaps), which finding seems to indicate that the disturbance concerns probably not only the enzymatic activity of the pancreas, but also the absorption of the end products of this digestion.

While the literature concerning studies of fat metabolism in this syndrome is quite large, but few papers deal with studies of the blood lipids, especially as regards their qualitative characteristics, and none were found which concern the degree of unsaturation of the fatty acids of the blood. Fanconi[2] was the first to study the blood lipids in this condition. He performed analysis of the blood and serum lipids by extraction with petroleum ether, which fraction he considered to be composed of neutral fat and free cholesterol. A decrease in the lipids of the petroleum ether extract of the blood was found, and this was said to be due mainly to lesser amounts of the free cholesterol fraction

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Material in this paper was abstracted from a thesis submitted by Doctor Luzzatti to the Graduate School of University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science.

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‡Department of Pediatrics, University of Texas School of Medicine, Galveston, Tex.

rather than to lesser amounts of the neutral fat. Because the values for blood cholesterol were directly proportional to the number of red blood cells, he believed this fall in free cholesterol might be explained by the decreased number of erythrocytes, which, he said, is a common finding in this disease. In addition, the values for the cholesterol ester were low all in the patients with the celiac syndrome. In analyzing the blood fat after ingestion of oil or butterfat, he could demonstrate no increase in the blood cholesterol in the patients with celiac syndrome such as usually occurred in his normal control subjects. The blood lipid curve following the fatty meal in these patients was flatter than that in normal individuals, and the peak was reached later (six hours instead of three hours). On the contrary, Bauer,[3] in studying the change in blood lipids after the ingestion of cream in one patient with celiac syndrome, found no difference in the values obtained as compared with those found in normal children. He fails to mention which method he employed for the determination of the blood lipids. Moncrieff and Payne[4] found values for the serum lipids ranging from 275 to 530 mg. per cent in six patients with celiac syndrome as compared with 142 to 208 in their normal subjects. Interpreting these findings in the light of the work of Hill and Bloor and others,[5] who thought the fecal fat for the most part to be fat excreted from the blood rather than unabsorbed fat, Moncrieff and Payne ascribed the steatorrhea to a "leaking" of fat from the blood into the intestine. On the basis of this conclusion these authors stated that the celiac syndrome is due not to a disturbance in fat absorption but rather to one in fat utilization and metabolism. Parsons[6] analyzed the blood fat in twenty-three patients with the celiac syndrome and found the values to be lower in these patients (average, 474 mg. per cent) as compared with those in thirty-four normal children (average, 618 mg. per cent). He also reported that the patients with the celiac syndrome, when given an emulsion containing 60 Gm. of olive oil, had a delayed rise in the blood fat values, and the whole curve was set at a lower level. After feeding 15 Gm. of dextrose he found no such increase in the blood fat as usually occurred in normal individuals. Parsons reported that as the child improves, the postabsorptive rise after fat ingestion should return to normal, but he gave no proof of this statement. From these few data on blood lipids in this condition it is evident that no conclusions can be reached. The fact that there is no uniformity in the findings of the various workers regarding the blood lipids in patients with celiac syndrome may well be explained in part at least by inadequacies and differences in the methods used.

Because of the paucity of information and the diverse findings concerning the blood lipids in this condition, it was felt that a more detailed study of the various fractions of the serum lipids should be made to determine whether or not any quantitative or qualitative difference is present in the various lipid fractions in patients with the celiac syn-

drome, regardless of the etiologic factor present. It seemed that fat absorption studies using fats with various degrees of unsaturation together with fat balance studies and fecal fat analysis might be helpful in the interpretation of the serum lipid findings in the patients with this condition. Furthermore it was believed that some knowledge concerning the relationship between certain fundamental processes of fat metabolism and the clinical symptoms characterizing this syndrome might be obtained. If it was found, as is usually assumed, that fat absorption is relatively low or absent in this condition, information might be obtained regarding two points; namely, whether the human body is able to synthesize fatty acids of high degree of unsaturation, and if not, what the reaction to this deficiency may be.

MATERIAL AND METHODS

The observations in this study were made on ten patients with the celiac syndrome. In four (Cases 1, 4, 5, and 6) the diagnosis of cystic fibrosis of the pancreas was proved at autopsy, and in two (Cases 2 and 3) this was the likely diagnosis, but in the other four (Cases 7, 8, 9, and 10) the etiology was not known. A brief summary of the clinical and laboratory findings concerning these patients is given in the case reports. Determination of the serum lipids was performed in eight patients with the celiac syndrome, using the microgravimetric method described by Wilson and Hansen,[7, 8] and the method used by Hansen[9] was employed for the separation of the acetone-soluble and acetone-insoluble fatty acids. Bloor's[10] method was used for the determination of total cholesterol and cholesterol esters. Studies of absorption of fat from the intestinal tract were made in eight of the patients following administration of 4 ounces of 35 per cent cream (iodine number = 20) and of a mixture composed of 150 c.c. of protein milk, 40 Gm. of corn oil (Mazola), and 20 Gm. of sugar (iodine number of corn oil = 120). The amount of fat in this mixture was about the same as that contained in the cream meal. From previous experience we did not believe that the extra carbohydrate of this mixture would affect the absorption of the oil. Blood was withdrawn before the meal, after a fast of from twelve to fourteen hours, and again four hours after the fatty meal. Previous experiments had shown that the peak in absorption usually is reached around the fourth hour after the ingestion of fat. Unpleasant reactions were not seen when the children were given these fatty meals, nor was the diarrhea increased. Studies of fat absorption after ingestion of cream were made with eight patients, whereas, due to the serious condition of many of these children, in only two subjects were we able to perform the study with the meal containing corn oil. Fecal fat analyses and fat balance studies were also carried out, employing Fowweather's[11] method with some modification for the stool analyses. We shall not report in detail concerning this phase of the study, our results being only a confirmation of the findings of previous workers;

however, we shall refer to the results in the discussion. In certain patients study of pancreatic function was made by examination of the duodenal contents following intravenous injection of secretin, one clinical unit of secretin per kilogram body weight being injected intravenously.

CASE REPORTS

CASE 1 (705526).—A. M., a 5-year-old female, was admitted to the University Hospital Feb. 16, 1941, because of repeated respiratory infections and recurrent episodes of diarrhea. The presence of oily stools and abdominal enlargement was noted shortly after birth. Because she was thought to have a "fat intolerance" when about 2½ years old, a low fat diet was advised. One month previous to admission she developed a severe upper respiratory infection with a marked cough and the production of profuse, thick, tenacious sputum. A younger brother also had symptoms of the celiac syndrome (Case 2, K. M.). Her weight was 12.7 kilograms on admission. She was rather pale, malnourished, and poorly developed for a child of 5 years, with cyanosis of the lips and fingernails and distinct clubbing of the fingers and toes. The lung fields were hyperresonant, and many coarse and crackling râles and rhonchi were heard especially over the bases posteriorly. The abdomen was distended and tympanitic. Urinalysis was negative. Hemoglobin, leucocyte, and differential white cell counts were normal and so were the blood urea nitrogen fasting blood sugar, plasma proteins, and cholesterol. The results of the stool examination are reported in Table I. Roentgenologic examination of the chest showed increased bronchovascular markings and findings consistent with bronchiolitis or some chronic fibrotic change. Films of the long bones revealed a mild degree of osteoporosis. Study of the pancreatic juice after the injection of secretin revealed the presence of 72 c.c. of material, but no evidence of amylase or lipase activity could be detected. The results of the oral glucose tolerance test were as follows: fasting, 103; ½ hour, 148; 1 hour, 126; 1½ hours, 106; 2 hours, 72 mg. sugar per 100 c.c. of blood. The results of the intravenous glucose tolerance test were as follows: fasting, 99; ¼ hour, 253; ½ hour, 186; 1 hour, 123; 1½ hours, 51; 2 hours, 103 mg. sugar per 100 c.c. of blood. Protein milk with 5 per cent banana powder and vitamin supplements were given, and pancreatin was prescribed. During her first stay in the hospital she had an episode of severe dyspnea and cough and was kept in an oxygen tent for nearly two months. She was discharged four months later only slightly improved. She was instructed to use a low fat, high protein, and high carbohydrate diet with vitamin supplements and pancreatin, 5 gr., three times daily. Her condition remained essentially unchanged, and in August of the same year she was readmitted to the hospital. At this time she had considerable respiratory distress with rapid, labored breathing and continuous coughing. The abdomen was large, tense, and shiny. There was marked pitting edema over the eyelids, ankles, legs, thighs, genitals, and sacral regions. Intense cyanosis was also present. Examination of the lungs revealed essentially the same findings as previously obtained. There was shifting dullness in the abdomen. Urine contained a trace of albumin, hemoglobin was 12.1 Gm., and leucocytes were 14,400 with normal differential count. Blood urea nitrogen was 17.8 mg. per cent; plasma proteins were 5.1 Gm. per cent, with albumin 2.0 and globulin 2.8. She was placed in an oxygen tent. Paracentesis was done, and 1,200 c.c. of clear fluid was removed. Plasma was given intravenously, and a mercurin suppository was used. Nevertheless the respiratory distress increased, and Aug. 16, 1941, she became listless, respiratory movements became more shallow and less labored, and she soon ceased.

The outstanding findings at autopsy were as follows: Between 1,500 and 2,000 c.c. of clear, straw-colored fluid were present in the peritoneal cavity. Dense pleural adhesions were found in the right apex and along the inferior margin of the right

lung, and large, dark red, firm lymph nodes occupied the hilar and mediastinal regions. A large amount of thick, yellowish, purulent material was present in the trachea and in both the larger and smaller bronchi. Both lungs showed crepitation and contained numerous firm areas throughout the substance, and on section multiple areas of thick yellowish material with occasional abscess formation were found. The liver was dark brown and firm with smooth capsule, and on section showed some evidence of congestion. The pancreas weighed 50 Gm., was firmer than usual, and densely adherent to the surrounding tissues. On section marked fibrosis was found to be present with very little pancreatic tissue in evidence. Microscopic examination of the lungs showed widely dilated bronchioles filled with polymorphonuclears and lymphocytes with peribronchial thickening due to infiltration into the walls and into the surrounding tissues. The pancreas showed large dilated ducts lined with mucinous epithelium, with no normal acinar tissue and few islets; marked fibrosis was evident throughout. The kidneys and the liver showed cloudy swelling, and the lymph nodes revealed lymphoid hyperplasia.

The final diagnosis was as follows: (1) celiac syndrome on the basis of a cystic fibrosis of the pancreas; (2) purulent bronchitis, bronchiectasis, bilateral bronchopneumonia; (3) cloudy swelling of liver and kidney; (4) generalized edema.

CASE 2 (680965).—K. M., a 2½-year-old male, was first seen in the Pediatric Outpatient Department of the University Hospital when he was 8 months old. The main complaint at that time was protruding abdomen, vomiting and bulky, light-colored, foul-smelling stools. He had had a voracious appetite since birth. Undigested material in the stool was first noticed when solid food was started. He had had bronchopneumonia at 6 months of age and another unclassified respiratory disease between the age of 9 months and 1 year. The only sibling in the family had proved cystic fibrosis of the pancreas (Case 1, A. M.). The child was admitted to the hospital for studies when he was 2½ years old. On admission his weight was 14.5 kilograms. He appeared to be a well-nourished child whose only finding was a large protruding abdomen. Urinalysis was negative. Hemoglobin, leucocytes, and differential white cell counts were normal, as was the serum calcium. The serum phosphorus was 2.9 mg. per cent. The examination of the stool is reported in Table I. The results of the oral glucose tolerance test were as follows: fasting, 68; ½ hour, 90; 1 hour, 107; 1½ hours, 131 mg. sugar per 100 c.c. of blood. The results of the intravenous glucose tolerance test were as follows: fasting, 81; ¼ hour, 287; ½ hour, 163; 1 hour, 132; 1½ hours, 90; 2 hours, 59 mg. sugar per 100 c.c. of blood. Blood amylase was 127 units and blood lipase, 0.4 c.c. N/20 NaOH. Barium enema showed some redundancy of the sigmoid colon. X-ray films of the chest and long bones were essentially negative. After completion of the special studies the child was placed on a low fat diet with vitamin supplements and pancreatin and was soon discharged. He was seen a number of times in the Pediatric Outpatient Clinic and seemed to be progressing quite well on this regimen. On Oct. 29, 1941, the serum phosphorus was 6.5 mg. per cent and the serum phosphatase, 33 Bodansky units. In the same month he developed moderately severe eczematous lesions in the face. In March, 1942, a duodenal drainage was performed for study of the pancreatic function following the injection of secretin. The amount of material collected in eighty minutes was only 6 c.c. The amylase content was 623 units per cubic centimeter of fluid for this eighty-minute period. This boy now is being followed in the outpatient dispensary. Pancreatin has also been discontinued and no change in fat excretion has been noted. The stools number from one to two daily, are soft and light colored, but do not contain an excess amount of fat.

The final diagnosis was (1) celiac syndrome, probably on the basis of a cystic fibrosis of the pancreas.

CASE 3 (670329).—E. C., a six-month-old female, was seen in the Outpatient Clinic of the Department of Pediatrics of the University Hospitals in July, 1938.

She was a premature infant who was breast fed for about three months and then given a cow's milk formula. She never gained satisfactorily but had had no vomiting or diarrhea. On admission her weight was 3,750 Gm. She was markedly undernourished, breathing was stridulous, and the abdomen was prominent. Urine was negative. She had a moderate anemia and an elevation of the white cell count. Plasma proteins and serum phosphorus were normal. The results of the stool examination are reported in Table I. X-ray films of the long bones showed some osteoporosis. During her stay in the hospital she developed bronchopneumonia, from which she recovered satisfactorily. She was discharged three months after admission with a weight gain of 1,400 Gm. She was readmitted Dec. 15, 1940, when 3 years old, because she had failed to gain weight and had had numerous greenish yellow, greasy stools. Three days before her second admission she developed edema. At this time she appeared undernourished and drowsy. Her weight was 10.9 kilograms, her height, 85 cm. She was rather pale, and generalized edema was noted. There was clubbing of the fingernails. The chest examination revealed some dullness and decreased breath sounds over both bases. Many medium-sized râles were scattered over both lung fields, especially in the left lower lobe. There was marked shifting dullness in the abdomen. Urine was negative. Hemaglobin was 11 Gm.; leucocytes and differential counts were normal. Hematocrit was 37 per cent; mean corpuscular volume, 93.6; mean corpuscular hemaglobin, 30.4; mean corpuscular hemaglobin concentration, 30.8. Blood urea nitrogen, plasma protein, and amino acid nitrogen were within normal limits. Results of the fecal fat analyses are reported in Table I. The results of the Exton and Rose's glucose tolerance test were as follows: fasting, 67; ½ hour, 100; 1 hour, 150 mg. sugar per 100 c.c. of blood. Blood amylase was 155 units. Vitamin B_1 excretion in twenty-four hours was 61 γ, and 78 γ on another occasion. The child was placed on a high protein, high caloric diet. The edema subsided; however, the course of the disease was progressively downhill. She failed to gain weight no matter what type of diet was employed, and toward the end of March, 1941, she developed a diffuse bronchiolitis with severe cough and cyanosis. Various therapeutic procedures were attempted but without success, and the child expired about four months after this second admission. Autopsy was not allowed.

The final diagnosis was (1) celiac syndrome probably on the basis of a cystic fibrosis of the pancreas, (2) bronchiolitis, and (3) generalized edema.

CASE 4 (705175).—D. A., a 9-month-old male infant, was admitted to the University Hospital Feb. 4, 1941, because of chronic diarrhea. From the ninth day after birth his stools were copious, foul, and foamy, and contained a large amount of undigested food. Several types of diets were tried at home, but his condition did not improve. One month prior to admission he developed an upper respiratory infection with light fever and marked cough. On admission his weight was 5,570 Gm. He was markedly dehydrated, and on crying severe cyanosis was present, and respirations were rapid and grunting. There was marked dullness over the entire right side of the chest with diminished breath sounds and many crackling râles. The abdomen was distended. Urine was normal. Hemoglobin, leucocytes, and differential white cell counts were normal. Blood amylase was 89 units. The fecal fat analysis is reported in Table I. Thoracentesis of the right side yielded 25 c.c. of thick, purulent material, which on culture showed coagulase positive staphylococci. After the fluid was removed an x-ray film of the chest revealed a diffuse mottling throughout both lungs, especially marked at the left base. This was of a nodular character and suggested either a capillary pneumonia or a bronchiolitis. Protein milk with banana powder as well as iron and vitamin supplements was started, and later pancreatin was added. Parenteral fluids, transfusions, and sulfathiazole were given, but the patient failed to respond and rapidly went downhill and expired sixteen days after admission.

The outstanding findings at autopsy were as follows: The right lung had many pleural adhesions, and on cut surface the lower lobe posteriorly showed congestion. Numerous bronchi in both lungs contained pus in the lumen. The liver was rather light in color, and on section the architecture appeared normal. Grossly, the pancreas was of normal appearance but was rather firm in consistency and on section appeared normal. Microscopic examination of the lungs showed the bronchi completely filled with polymorphonuclear cells, which also infiltrated the walls. The liver showed a central atrophy of the cords with pale staining cells not containing fat. The pancreas showed a moderately severe chronic intralobular and interacinar fibrosis.

The final diagnosis was (1) celiac syndrome on the basis of a cystic fibrosis of the pancreas, (2) purulent bronchitis, and (3) pleural adhesions.

CASE 5 (659218).—S. J., a 3-year-old female, was admitted to the University Hospitals Sept. 24, 1940, because of chronic diarrhea and prolapse of the rectum. The patient had loose stools, even when being nursed, and they continued to be copious, fatty, and foul smelling. At times food did not seem to be digested, and occasionally blood and mucus were noted in the stools. None of the dietary regimens employed seemed to remedy the condition. On admission she appeared markedly undernourished, her weight was 8.9 kilograms, and her length, 84 cm. The lungs were clear and the heart normal. The only positive physical finding was a diffusely large abdomen. There was a prolapse of the rectum which was easily reducible. Urine was negative. Hemoglobin was 7.8 Gm., which rose to 14 Gm. after several transfusions; leucocytes varied from 8,000 to 36,000 with normal differential white cell counts. Blood urea nitrogen was 13.6 mg. per cent; carbon dioxide combining power, 29 volumes per cent, subsequently brought to 47 volumes per cent by parenteral fluids; blood chlorides, 590 mg. per cent, increasing later to 652 mg. per cent; serum calcium, normal; serum phosphorus, 3.1 mg. per cent; plasma proteins, normal. There was no free hydrochloric acid in the stomach on fasting, but free hydrochloric acid was present after histamine stimulation. The results of the oral glucose tolerance test were as follows: fasting, 94; ½ hour, 99; 1 hour, 155; 1½ hours, 173; 2 hours, 196 mg. sugar per 100 c.c. of blood. The fecal fat analysis is reported in Table I. X-ray films of the long bones showed a mild degree of osteoporosis. Barium enema showed marked dilatation of the entire colon, the sigmoid being enormously dilated. The child was given a high protein, high carbohydrate, and low fat diet, but in spite of gavage feeding she failed to gain weight. Subsequently she developed an infection of the lungs which resisted all types of therapy. Repeated films of the chest revealed a progressive pneumonic process in both lungs, and multiple cysts especially in the right lung were suggested by the appearance of the lung fields. These were thought to be probably secondary to the inflammatory process. The course of the disease was generally downhill, although the child's condition did not seem to be much worse on the day she expired.

The outstanding findings at autopsy were as follows: There was marked distension of the colon and stomach. The pleural cavities contained a number of adhesions, and the surface of both lungs contained a number of palpable areas of consolidation, chiefly in the lower lobes. On section numerous areas of yellowish white, slightly raised foci were encountered, and free pus was expressible from the small bronchi and bronchioles. Also in the left lung numerous thin-walled cystic cavities were noted. The trachea showed intense hyperemia and was filled with turbid, reddish brown, thick fluid. The liver had a light yellow color, the surface was smooth, and on section appeared to be extremely pale and soft with no distinct architectural markings. The pancreas had a smooth surface, was lobular, and grossly contained cysts. Microscopic examination of the lungs showed dilated bronchi filled with pus with destruction of the epithelium at some points and considerable mucus in the cells in others. The walls were replaced by chronic granulation tissue,

and in one section the alveolar septa were thick and fibrous. The alveoli had occasional fibrin plugs, serum, lymphocytes, and numerous large macrophages, some of which were filled with fat; and in some areas multiple accumulation of polymorphonuclears equivalent to abscess formation was noted. The liver showed a diffuse fatty metamorphosis. The pancreas showed complete replacement of the acinar tissue by fibrous tissue with only a few slight cystic ducts, a number of islands, and occasional acinar remnants. The whole fibrous structure was embedded in fat.

The final diagnosis was as follows: (1) celiac syndrome on the basis of a cystic fibrosis of the pancreas; (2) purulent bronchitis, bronchopneumonia, and bronchiectasis; (3) fatty metamorphosis of the liver.

CASE 6 (706209).—E. S., a 1-year-old female, was first seen in the Outpatient Clinic of the Department of Pediatrics of the University Hospital in March, 1941. At 6 months of age she was admitted to the Minneapolis General Hospital because of an attack of pneumonia. She was critically ill at that time but responded fairly well to chemotherapy. One month later x-ray films of the chest showed atelectasis of the right upper lobe. Following this illness the stools became bulky, gray, foul smelling, and frequent and were noted to contain undigested food. A low fat, high protein, and high carbohydrate diet was given, but this did not change the consistency of the stools. A glucose tolerance test at that time showed the following: fasting, 50; ½ hour, 90; 1 hour, 80; 2 hours, 75; 3 hours, 55 mg. sugar per 100 c.c. of blood. Serum amylase was 22 units. When she was examined in the Outpatient Clinic at the University Hospital her weight was 7,080 Gm. Because various changes in the diet did not improve her condition, she was admitted July 1, 1941. On admission her weight was 7,700 Gm. She appeared pale and undernourished, and a fine papular rash over the face and forehead and a macular eruption over the buttocks and lower back was discernible. Outside of these findings the physical examination was negative. Urine was negative. Hemoglobin was 11.4 Gm.; the leucocytes and differential white cell counts were normal. The results of the oral glucose tolerance test were as follows: fasting 73; ½ hour, 100; 1 hour, 84; 2 hours, 111; 3 hours, 66 mg. sugar per 100 c.c. of blood. The results of the intravenous glucose tolerance test were as follows: fasting, 72; ¼ hour, 187; ½ hour, 135; 1 hour, 78; 1½ hours, 93; 2 hours, 95 mg. sugar per 100 c.c. of blood. The serum calcium, phosphorus, and phosphatase were normal. The acid content in the stomach was normal. The fecal fat analysis is reported in Table I. X-ray films of the chest showed some expansion to have taken place in the right upper lobe. Roentgenograms of the long bones were negative. On July 8 the infant developed what was considered to be a capillary pneumonia with secondary emphysema. These findings remained consistent throughout her stay in the hospital, and repeated x-ray examinations of the lungs showed no change to have occurred. She was discharged July 20 without marked improvement. On Nov. 17, 1941, she was readmitted to the hospital because she had developed anorexia, dyspnea, and cyanosis about ten days previously. The patient had not gained any weight in this four-month interval. Examination at this time revealed a poorly developed and malnourished 2-year-old girl who was in moderately acute distress with dyspnea. Cyanosis of the lips and fingernails with a moderate degree of clubbing of the fingers was noted. Breathing was abdominal in character, and there was intermittent retraction of the suprasternal notch. Coarse inspiratory râles were heard throughout both lung fields. X-ray films of the chest revealed increased density and the presence of miliary nodules throughout both lungs. The results of the oral glucose tolerance test were as follows: fasting, 113; ½ hour, 172; 1 hour, 186; 2 hours, 150; 3 hours, 140 mg. sugar per 100 c.c. of blood. The patient was discharged Dec. 1, 1941, without gain in weight and only slight general improvement. She was readmitted to the hospital Feb. 23, 1942. During this interval she had been doing quite well but had a persistent cough with occasional production of stringy mucoid material. The child went home after two days in fairly

comfortable condition. However, the respiratory symptoms became increasingly severe, and she expired March 5, 1942.

The outstanding findings at autopsy were as follows: Severe purulent bronchitis and patches of bronchopneumonia were present throughout both lungs. Thick purulent material could be expressed from the cut surface of both lungs throughout all lobes. The liver showed marked yellow discoloration. The pancreas appeared somewhat smaller than normal and it was firmer than usual, but no cysts were found on gross examination. Microscopic examination of the lungs showed bronchiectasis, purulent bronchitis, and marked peribronchitis; there were some areas of thickening of the bronchial walls with lymphocytic infiltration and scattered areas of emphysema. The liver showed marked fatty metamorphosis. The pancreas revealed marked fibrosis with great reduction of the normal acinar tissue and cystic dilatations of the ducts and normal island tissue.

The final diagnosis was as follows: (1) celiac syndrome on the basis of a cystic fibrosis of the pancreas; (2) purulent bronchitis, bronchopneumonia, and bronchiectasis; (3) fatty degeneration of the liver.

CASE 7 (715446).—J. R., a 1-year-old male, was admitted to the University Hospital Dec. 22, 1941, because he had had projectile vomiting during the three previous weeks. He had had a somewhat similar episode at the age of 6 weeks, which lasted until he was 3 months of age. He had always been below average in weight, but neither diarrhea nor fatty stools were noticed. On admission his weight was 7.7 kilograms. On examination he was found to be a small, malnourished child, extremely irritable, and crying constantly. There was a soft blowing systolic murmur over the apical region, and a moderately distended abdomen was noted. Urinalysis showed only a trace of acetone on admission. The hemoglobin averaged between 11.6 and 15.5 Gm., and the leucocytes and differential white cell counts were normal. Plasma proteins varied from 4.9 to 7.0 Gm. per cent, with a normal albumin globulin ratio. The carbon dioxide combining power varied from 30 to 48 volumes per cent. The blood urea nitrogen was normal. The blood vitamin C level was 0.137 mg. per cent. Serum calcium was 9.5 mg. per cent; serum phosphorus, 3.1 mg. per cent; serum phosphatase 11.4 Bodansky units. The results of the oral glucose tolerance test were as follows: fasting, 74; ½ hour, 84; 1 hour, 84; 2 hours, 84; 3 hours, 78 mg. sugar per 100 c.c. of blood. This was repeated July 14 with the following result: fasting, 76; ½ hour, 77; 1 hour, 85; 2 hours, 125; 3 hours, 100 mg. sugar. The results of the intravenous glucose tolerance test were as follows: fasting, 72; ½ hour, 144; 1 hour, 72; 2 hours, 73; 3 hours, 88 mg. sugar. The fecal fat analysis is reported elsewhere (Table I). X-ray films of the chest were negative, while films of the long bones showed slight decalcification. Barium meal showed the barium in the descending colon five hours after administration; at that time there was an abnormal distribution of the barium within the small bowel with clumping of material. The total amount of duodenal juice obtained during an eighty-minute period after the injection of secretin was 35 c.c. and contained amylase, 745 units, lipase, 46.9 c.c. N/20 NaOH per cubic centimeter of fluid. The baby was put on a high caloric diet of the celiac type with added vitamin supplements. The course during the first month was not too satisfactory in that he failed to gain weight and he continued to be very irritable and to have steatorrhea. It was not until the third month that he had been on the same diet that he began to be more cheerful, and rather suddenly he started to gain weight again. He was discharged March 26, 1942, after he had gained 3 kilograms in weight.

The final diagnosis was celiac syndrome, unknown etiology.

CASE 8 (719018).—J. F., an 8-month-old baby boy, was admitted to the University Hospital April 13, 1942, because of vomiting and diarrhea. He was a premature infant weighing only 5 pounds, 6 ounces, at birth. The baby began to vomit soon

after artificial feedings were started, during the second month of life. When 4 months old he began to have large, light-colored, foul-smelling stools. Associated with these symptoms, abdominal distension developed. On admission the weight was 5,450 Gm. The baby was undernourished, and a fine macular rash over the arms and trunk was noted. The most marked physical finding was a protuberant, tympanitic abdomen. Urine was negative. The hemoglobin was 11.2 Gm., and the leucocytes and differential white cell counts were normal. Coagulation time was 4 minutes, 45 seconds, bleeding time, 2 minutes 15 seconds. Serum calcium, phosphorus, and phosphatase were normal. The vitamin C level in the blood was 0.135 mg. per cent. Plasma proteins were normal. The fecal fat analysis is reported in Table I. The total amount of pancreatic juice obtained during eighty minutes after the injection of secretin was 29 c.c. and contained amylase, 674 units, lipase, 627 c.c. N/20 NaOH per cubic centimeter of fluid. The baby was placed on a routine nursery formula with vitamin supplements. He was discharged June 20, 1942, after a gain of approximately 2 kilograms.

The final diagnosis was celiac syndrome, unknown etiology.

CASE 9 (722698).—L. K., 14-month-old baby boy, was admitted to the University Hospital Aug. 10, 1942, because since birth he had from six to seven bowel movements a day and these were usually large, foul smelling, loose, and oily, and often contained undigested food. He was a premature infant, and had been breast fed for two months. He had eaten fairly well but had never gained weight. Several different types of foods were tried without any change in the type of stools or in the weight curve. He had had repeated respiratory infections. Ten days before admission he developed another respiratory infection with temperature over 103° F. (rectally) together with severe anorexia and diarrhea. The family history revealed that a 5-year-old sister had died two years previously of bronchiectasis; and this child had had the same type of stools following a bronchopneumonia at the age of 9 months. On admission the baby was rather pale and malnourished; his weight was 8.5 kilograms. The pharynx was inflamed, and the right eardrum appeared injected. The abdomen was enlarged. Urine was negative. The hemoglobin was 10.9 Gm., and the leucocytes and differential white cell count were normal. The fecal fat analysis is reported in Table I. A celiac type of diet was started, and the child after completion of the blood lipids studies was discharged from the hospital.

The final diagnosis was celiac syndrome, unknown etiology, possibly on the basis of a cystic fibrosis of the pancreas.

CASE 10 (722825).—N. E., a 3-month-old male infant, was admitted July 29, 1942, because of cough and emaciation. He was a full-term baby and weighed 7 pounds, 6 ounces at birth. At the end of the first month of life the baby developed a hacking cough. Associated with the cough there was also vomiting and a marked loss in weight. Since birth he had had bulky, foul-smelling, pale, cheesy looking stools, at least four per day. Changes in the diet had not brought any improvement in his condition. The family history was negative. On admission his weight was 3,200 Gm., his length, 57 cm.; he was undernourished, dehydrated, and very irritable and had a hacking cough. The skin was pale. The chest showed an increase of the anteroposterior over the transverse diameter. There was no dullness on percussion; there were coarse râles throughout both lung fields posteriorly. The abdomen was distended and the liver was slightly enlarged. Urinalysis was negative. Hemoglobin was 7.7 Gm.; white cells and differential counts were normal. Blood urea nitrogen was 11 mg. per cent and the carbon dioxide combining power, 72 volumes per cent. Plasma proteins were 5.2 Gm. with albumin 2.6 and globulin 2.4. The blood Wassermann was negative. X-ray films of the long bones were negative, whereas those of the chest showed fibrosis radiating out from the hili toward the

periphery, especially marked on the right. The baby was put on a routine formula until the studies were completed and subcutaneous fluids and transfusions of blood and plasma were given. The fecal fat analysis is reported in Table I. A glucose tolerance test gave the following result: fasting, 41; ½ hour, 83; 1 hour, 68; 2 hours, 69 mg. sugar per 100 c.c. of blood. The serum calcium was 9.6 mg. per cent; phosphorus, 4.7 mg. per cent. Ten days after admission the baby was given a formula composed of casein hydrolysate and dextrimaltose, and 5 gr. of pancreatin were also given before each feeding. Fifty thousand units of vitamin A and 1 c.c. of vitamin B complex (Bejectal) were administered intramuscularly daily, and vitamin supplements were also given orally. The baby also received 0.1 Gm. sulfadiazene every four hours daily. On this treatment he gained about 1½ pounds. However, about one month after admission he developed increasing difficulty in respirations and became edematous and cyanotic. The course from this time on was rapidly downhill, and the baby died about five weeks after admission. Autopsy was not allowed.

Final diagnosis was (1) celiac syndrome, unknown etiology, possibly on the basis of a cystic fibrosis of the pancreas; (2) pulmonary fibrosis and bronchitis; (3) generalized edema.

TABLE I

FECAL FAT ANALYSIS IN TEN PATIENTS WITH CELIAC SYNDROME

CASE	AGE	DATE	DIET	DRY MATTER % WET WEIGHT	TOTAL FAT % DRY MATTER	SOAPS % DRY MATTER	FREE FATTY ACIDS % DRY MATTER	NEUTRAL FAT % DRY MATTER	UNSPLIT FAT % TOTAL FAT
1	5½ yr.	2/19/41	Low fat	22.0	27.7	15.8	9.2	2.7	9.7
2	2½ yr.	4/ 7/41	Regular	26.4	38.4	None	31.6	6.9	17.8
3	2½ yr.	1/29/41	Regular	35.7	34.8	None	9.1	27.6	79.2
4	10 mo.	2/ 7/41	Regular	30.7	42.0	25.5	12.3	4.1	9.8
5	3½ yr.	9/30/40	Regular	40.6	78.5	22.0	44.4	6.7	8.5
6	12 mo.	11/ 6/40	Low fat	29.4	12.6	4.9	6.4	1.2	10.0
7	14 mo.	12/31/41	Regular	18.0	48.3	–	–	–	–
8	8 mo.	4/14/42	Regular	25.4	37.9	31.9	4.1	2.1	5.6
9	14 mo.	7/28/42	Low fat	25.9	27.5	None	18.9	8.9	32.0
10	3 mo.	2/ 6/42	Regular	16.3	49.4	0.8	26.0	22.6	46.5
Normal mean values given by Fowweather[11]			Regular	21.0	17.5	4.6	5.6	7.3	42.0
Mean of our control subjects			Regular	22.1	19.4	10.2	4.4	4.7	23.1

RESULTS

The results of the serum lipid analysis are reported in Table II and those of the fat absorption studies are reported in Table III.

COMMENT

The quantity of the total fatty acids in the serum under fasting conditions in the patients suffering from the celiac syndrome ranged from 260 to 374 mg. per 100 c.c., with an average of 311 mg. for the twelve determinations (Table II). The values for the acetone-soluble fraction (cholesterol ester plus neutral fat fatty acids) varied from 144 to 249 mg. per 100 c.c., while those for the acetone-insoluble fraction (phospholipid fatty acids) varied from 64 to 133 mg. The total cholesterol varied from 79.5 to 213 mg. per 100 c.c., the esters being from 53.8 to

TABLE II

VALUES FOR THE VARIOUS FRACTIONS OF THE SERUM LIPIDS AND THE IODINE NUMBERS OF THE FATTY ACIDS OF THESE FRACTIONS IN EIGHT PATIENTS WITH CELIAC SYNDROME AND IN FIVE CONTROL SUBJECTS

CASE	AGE	DATE	TOTAL FATTY ACIDS		ACETONE-SOLUBLE FATTY ACIDS		ACETONE-INSOLUBLE FATTY ACIDS		CHOLESTEROL		
			MG. %	I.N.*	MG. %	I.N.	MG. %	I.N.	TOTAL MG. %	ESTER MG. %	FREE MG. %
A. Patients With Celiac Syndrome											
2	2½ yr.	4/30/41	341.2	–	205.3	–	74.1	–	–	–	–
		5/26/41	350.1	80.6	223.7	64.1	132.9	70.9	–	–	–
		3/ 9/42	351.9	77.8	219.1	74.5	106.3	77.7	134.3	72.4	61.9
3	2½ yr.	2/10/41	260.0	70.7	144.4	69.2	114.6	57.5	–	–	–
5	3½ yr.	10/12/40	260.8	83.5	186.1	82.7	74.1	83.3	164.3	105.9	58.4
6	20 mo.	7/ 3/41	356.9	78.1	249.2	75.0	101.8	–	–	–	–
		2/24/42	274.4	77.0	199.1	76.0	64.0	82.3	79.5	–	–
7	15 mo.	1/13/42	376.1	70.1	242.0	71.7	121.5	73.1	–	–	–
	17 mo.†	3/21/42	373.0	101.5	232.2	102.1	131.8	104.3	213.0	128.8	84.2
8	8 mo.	4/17/42	264.9	75.6	171.8	75.4	83.5	76.2	152.7	97.0	55.7
9	14 mo.	7/31/42	281.3	75.5	208.5	74.3	72.1	51.8	145.0	–	–
10	3 mo.	8/21/42	308.0	86.5	218.7	83.0	81.3	89.4	117.6	–	–
B. Control Subjects											
1	17 mo.	1/18/40	456.7	113.2	315.3	101.5	120.0	114.0	–	–	–
2	17 yr.	5/24/40	293.5	113.5	201.5	107.4	89.9	118.0	–	–	–
3	2 yr.	11/28/40	353.0	103.7	244.2	99.4	95.2	106.8	–	–	–
4	7 mo.	6/ 9/39	300.0	98.0	199.0	91.0	84.0	123.0	–	–	–
5	1 yr.	1/21/38	384.0	101.0	242.0	94.0	110.0	106.0	–	–	–

*I.N., Iodine number.
†Clinically improved.

TABLE III

VALUES OF THE VARIOUS FRACTIONS OF THE SERUM LIPIDS AND THE IODINE NUMBERS OF THE FATTY ACIDS OF THESE FRACTIONS IN PATIENTS WITH THE CELIAC SYNDROME BEFORE AND FOUR HOURS FOLLOWING THE ADMINISTRATION OF A FATTY MEAL

CASE	AGE	DATE	TOTAL FATTY ACIDS		ACETONE-SOLUBLE FATTY ACIDS		ACETONE-INSOLUBLE FATTY ACIDS		CHOLESTEROL		
			MG. %	I.N.*	MG. %	I.N.	MG. %	I.N.	TOTAL MG.%	ESTER MG. %	FREE MG. %
1. Following Administration of 4 Ounces of 35 Per Cent Cream											
2	2½ yr.	4/30/41	341.2	–	205.3	–	74.1	–	–	–	–
			298.2	–	175.0	–	84.4	–	–	–	–
3	2½ yr.	2/10/41	260.9	70.7	144.4	69.2	114.6	57.5	–	–	–
			293.2	60.6	156.5	68.4	109.2	58.5	–	–	–
5	3½ yr.	10/12/40	280.8	83.5	186.1	82.7	74.1	83.3	164.3	105.9	58.4
			184.3	81.6	190.5	–	107.6	80.3	147.9	101.2	46.7
6	20 mo.	7/ 3/41	356.9	78.1	249.2	75.0	101.9	–	–	–	–
			462.8	72.1	322.6	–	147.0	–	–	–	–
7	15 mo.	1/13/42	374.1	70.1	242.0	71.7	121.5	73.1	–	–	–
			573.4	65.2	407.7	62.3	149.3	70.2	–	–	–
9	8 mo.	4/17/42	264.9	75.6	171.8	75.4	83.5	76.2	152.7	97.0	55.7
			1306.8	45.0	1173.5	42.5	100.2	67.3	162.9	101.6	61.3
9	14 mo.	7/31/42	281.3	72.1	208.5	75.5	72.1	51.8	145.0	–	–
			272.5	74.2	194.2	76.6	76.5	59.6	145.8	–	–
10	4 mo.	8/21/42	308.0	86.5	218.7	83.0	81.3	89.4	117.6	–	–
			346.0	83.6	233.2	80.7	91.2	89.9	120.8	–	–
2. Following Administration of an Emulsion Containing 40 Gm. of Corn Oil											
2	2½ yr.	5/26/41	350.1	80.6	223.7	64.1	132.9	70.9	–	–	–
			338.5	69.9	239.4	64.1	140.5	61.0	–	–	–
7	17 mo.	3/21/41	373.0	101.5	232.2	102.1	131.8	104.3	213.0	128.8	84.2
			463.4	107.1	313.0	108.4	143.4	106.6	197.5	94.6	102.9

*I.N., Iodine number.

68.1 per cent of the total. All these values are within the normal range of variability with the exception of one case with rather low serum total cholesterol. These data indicate that the *quantitative* values for the total lipids and the various lipid fractions in the serum are essentially normal in the patients with the celiac syndrome. In distinct contrast to the normal findings for the quantitative values of the blood lipids, a definite alteration was found in the degree of unsaturation of the fatty acids in all the fractions in the patients with this condition. The iodine numbers of the total fatty acids in the patients with celiac syndrome varied between 70.7 and 86.5 (the value of 101.5 in Case 7 was obtained at the time of clinical improvement), whereas in the control subjects these values ranged between 98 and 113.5, which values correspond to those reported previously for a group of normal control subjects and of patients having various pathologic conditions not related to disturbance of fat metabolism. It is interesting to note that in this early report made by Hansen[8] the only subject in his control group of patients with various pathologic conditions who had a low iodine number of the serum fatty acids was a child suffering from the celiac syndrome. The fatty acids in the acetone-soluble fraction had iodine numbers ranging from 64.1 to 82.7, while those in the acetone-insoluble fraction had values from 57.5 to 83.3. These values are much lower than those found in control subjects in this study and also much lower than those found during current investigations in this laboratory.[12] It is therefore evident that a striking abnormality is present in the *qualitative* characteristics of the serum fatty acids in this condition. It is worth noting here the fact that in the patient who apparenly recovered (Case 7), the iodine number of the fatty acids in the various fractions of the serum returned to normal.

The absorption of fat from the intestinal tract as measured by serum lipid values before and four hours after the ingestion of cream or the emulsion of corn oil was not consistent in our cases (Table III). This is not surprising when one considers the numerous factors which may interfere with an absorption curve of this kind. In five patients (Cases 2, 3, 5, 9 and 10) there was no rise in the serum lipid values four hours after the ingestion of cream. That no absorption was present in these patients is further evidenced by the fact that no significant decrease in the iodine number of the fatty acids occurred, as one would have expected were the cream absorbed. There was also no change in cholesterol and cholesterol esters where these determinations were made. On the other hand, in three patients an increase in the serum lipids occurred. One patient (Case 6) showed a slight increase of the serum fatty acids after the ingestion of cream, while another (Case 7) had a normal increase, and in still another (Case 8) the increase was many times that which is considered normal. The decrease of the iodine number in these patients corresponded to the low degree of unsaturation of the fat administered. It seems that absorption of fat was best in

the two patients in whom the diagnosis of cystic fibrosis of the pancreas was considered to be unlikely.

In experiments where an unsaturated type of fatty acid was given the results again were variable (Table III). In one patient (Case 2) there was no absorption of corn oil as demonstrated by the fact that there was neither an increase in the serum lipid values nor did the iodine number change in the direction of the higher iodine number of the fat administered. The situation was somewhat different in Case 7; here an increase in the fatty acid values occurred in the patient following the administration of the emulsion containing the corn oil, and the iodine numbers of the fatty acids in the various fractions changed according to the degree of unsaturation of the fat fed. The changes observed in the serum lipids of both these patients however, were similar, so far as the postabsorptive rise is concerned, to those obtained when they were given cream as a source of fat.

DISCUSSION

Of the ten children studied, six were considered to have a cystic fibrosis of the pancreas; in four (Cases 1, 4, 5, and 6), typical changes in the pancreas were found at autopsy. In one (Case 3), autopsy was not performed but clinical symptoms and the unusual finding of a large amount of unsplit fat in the stool suggested the same diagnostic possibility. In the other (Case 2), who is still alive, this diagnosis was suggested because of the family history (the older sister had proved cystic fibrosis of the pancreas) and because of the small amount of pancreatic juice and enzymatic activity in this material obtained after the injection of secretin. Of the four remaining cases, two of the patients (Cases 7 and 8) were considered unlikely to have cystic fibrosis of the pancreas, one of them recovered, and the other is still under observation. The other two (Cases 9 and 10) were considered possibly to have a cystic fibrosis of the pancreas because of the family history in one (Case 9) and the pulmonary pathology in the other (Case 10). The first of the two is still under observation; the second died, and unfortunately no autopsy was allowed.

In all of these patients, irrespective of the cause of the disturbance, the serum lipid values were within the normal range. In both the patients with celiac syndrome and the control subjects the quantitative values are essentially the same for all the lipid fractions, total fatty acids, acetone-soluble fatty acids, acetone-insoluble fatty acids, total cholesterol, cholesterol esters, and free cholesterol (Table II). These findings seem to indicate that the body is able to maintain to a certain extent a normal blood fat level even when absorption from the intestinal tract is greatly reduced for a considerable period of time, as occurs in subjects with this disorder. In contrast with the normal finding for the quantitative values of all the lipid fractions, there was a definite decrease in the degree of unsaturation of the fatty acids in all the different fractions

(Table II). As there is evidently no increase in saturated fatty acids, this decrease would suggest that the highly unsaturated fatty acids, mainly linoleic and arachidonic acid, are decreased in all the lipid fractions.

In most of the patients (five of eight) there was no increase in the serum fatty acids following the administration of a fatty meal, showing that a fundamental disturbance in fat absorption was present. One patient showed a slight absorption and in two cases, a normal increase in blood fat occurred. It happened that these two latter patients were considered unlikely to have a cystic fibrosis of the pancreas. In order to explain the irregular findings in the absorption curves it is important to remember that many factors have to be taken into consideration in interpreting such curves; for instance, rate of emptying of the stomach, motility of the digestive tract, absorptive capacity of the intestine at the particular moment of the experiment, time interval of the withdrawal of the second blood specimen which may not correspond to the peak of fat absorption, and more or less rapid depositon or utilization of the absorbed fat, as well as the size and even the nutritional status of the patient.

The two abnormal findings, namely, the low iodine number of the serum fatty acids and the flattened absorption curves, cannot be entirely explained with the present knowledge of physiology of fat metabolism. Inasmuch as it has been shown that experimental animals maintained on a fat-free diet have decreased iodine numbers of the serum fatty acids,[13-18] it may well be that the low iodine number of the fatty acids found in our patients can be explained by the poor absorption of fat from the intestinal tract, as poor absorption would cause a condition which approximates maintenance on a low fat diet. In this way the reserve of unsaturated fatty acids in the body would be exhausted. It may be well to point out again that the low values for the iodine number of the fatty acids were found in the patients with the celiac syndrome, whether they were on low fat diet or on a normal fat intake. On the contrary, patients with the celiac syndrome in the recovery stage, even when maintained on a low fat diet, are found to have iodine numbers of the serum fatty acids which are in the normal range. Burr and others[19, 20, 21] have shown that careful exclusion of fat from the diet of rats leads to development of scaly skin, caudal necrosis, marked retardation of growth, kidney lesions with hematuria, and early death. Animals suffering from these abnormalities were found by Hansen and Burr[13] to have a decrease in the iodine number of the fatty acids of the serum. This fact is undoubtedly due to the inability of the animal organism to synthetize the so-called essential unsaturated fatty acids. Very little is known about unsaturated fatty acid deficiency in other species. Hansen and Wiese,[18] in experiments under way in this laboratory, have shown that puppies reared on a low fat diet develop distinct skin changes and that the iodine number of the fatty acids of the serum

decreases as compared with the iodine number for animals given the same diet except for the substitution of lard for 28 per cent of the calories supplied by sucrose. Still fewer studies of blood lipids have been made on human subjects maintained on diets extremely low in fat. Brown and co-workers[17] studied various features, including the behavior of the blood lipids of a human subject who maintained himself on a low fat diet for a period of six months. The iodine number of the serum fatty acids was definitely decreased, and the arachidonic and linoleic acid content of the serum lipids fell to about 50 per cent of the level which was found when he was maintained on a normal diet. No skin lesions or loss of weight occurred in this adult subject.

Another factor which is known to influence the iodine number of the serum lipids is infection. It is well known that patients with the celiac syndrome suffer repeated infections, especially of the respiratory tract. However, it does not appear that this is the cause of the low iodine values in our patients. The iodine numbers reported by McQuarrie and Stoesser[22] and by Stoesser[23] in acute infections were not as low as those found in our patients. It is also possible that the impaired liver function commonly associated with this condition may have an effect on the degree of unsaturation of the blood lipids. Just how significant a role the liver plays in this respect is not known. It seems, therefore, that the best interpretation of the low iodine number of the fatty acids in patients suffering from the celiac syndrome simply is that this low iodine number results from the prolonged impaired absorption of fat. These low iodine values suggest that highly unsaturated fatty acids (mainly arachidonic and linoleic acid) are not synthesized by the human organism. It is well known that they are not synthesized by rats.[21] With the poor absorption of fat from the intestine the unsaturated fatty acids may become depleted from the body. In the patient (Case 7) who recovered, with the resumption of fat absorption, the iodine number of the serum fatty acids promptly returned to normal, which would seem to substantiate the interpretation that the faulty absorption causes the low degree of unsaturation of the serum lipids. In this patient the iodine number of the fatty acids of the serum was 70.1 at the time when the gain in weight was unsatisfactory. After a period of three months on the celiac type of diet the child started gaining weight and the general appearance improved; at this time the iodine number of the total fatty acids of the serum had risen to the normal level of 101.5 even though he was still on a low fat diet. Recently this same phenomenon was found to occur in an 8-year-old girl with malnutrition and steatorrhea in whom a diagnosis of celiac syndrome of unknown etiology was made. This child improved markedly under appropriate dietary regimen and administration of vitamin B complex and liver extract parenterally. The iodine number of the serum fatty acids shortly after admission was 76.5. When she appeared definitely improved clinically the iodine number

rose to 103, in spite of the fact that she had been kept for about four months on a relatively low fat diet. The same finding was seen in a 13-month-old infant. These two patients came to the hospital subsequent to the time this study was made and therefore the cases are not reported here. These findings suggest that an early and yet relatively simple means of detecting signs of improvement of fat absorption in this disease may be the determination of the iodine number of the serum fatty acids. This seems to be especially significant when the patients have been maintained on a low fat diet for a long period of time. In such instances as these, the fecal fat analyses do not give reliable information unless balance studies are undertaken at the same time. For example, in one of the cases reported (Case 6), one could consider the finding of 12.6 total fat per cent of dry matter in the stool as within the normal range if one were not aware of the fact that the child was on a low fat diet. In a condition of low fat intake these children do not show steatorrhea in the true sense of the word; that is, the amount of total fecal fat is not above the actual range of normal values. In these patients a determination of the iodine number of the serum fatty acids appears to show the abnormality in fat absorption quite clearly, as the iodine number is low when the fat is not normally absorbed. In the aforementioned case the iodine number of the serum fatty acids was 78.1.

Whether the deficiency of unsaturated fatty acids present in this condition is significant in interpreting some of its symptoms (skin eruptions, failure to gain weight) or not is difficult to say. One must be careful in interpreting these findings, because the impaired absorption of fat and vitamins itself could explain some of these abnormalities. More extensive investigation in the field of the unsaturated fatty acid deficiency in human beings is necessary before one will be able to evaluate correctly these findings.

Even more difficult to explain is why fat is not absorbed properly. This does not seem to be due entirely to a lack of enzymes, as the fat in the intestinal tract is split by the intestinal lipase. This splitting is evidenced by fecal fat analysis. The disturbance of absorption seems to be the main alteration, even in those patients with the celiac syndrome associated with a cystic fibrosis of the pancreas. Several factors are concerned with fat absorption in normal subjects. These are as follows: (1) type of fat ingested (molecular weight, degree of unsaturation and of molecular dispersion and emulsification); (2) gastric motility and emptying time of the stomach; (3) gastric lipase; (4) bile salts; (5) pancreatic enzymes; (6) intestinal lipase; (7) phosphorylation in the intestinal mucosa; (8) condition of the intestinal lymphatic system. Each of these factors may contribute to the interference with fat absorption resulting in steatorrhea. The first four of these seem not to play a role in the celiac syndrome. The pancreatic enzymes, the fifth factor, are often lacking, but their function in regard to fat-

splitting effect seems to be taken over by the intestinal lipase at least to some extent in almost every instance. The importance of the phosphorylation on the absorption of the fatty acids is a question which still is unsolved, and one cannot weigh the possibility of this factor being associated with the celiac syndrome until further investigations have been made. Also the importance of the adrenals in this process of phosphorylation as maintained by Verzar[24] and his school is even a more controversial point, even if this author has experimentally produced in animals a condition, which, he says, is similar to the celiac syndrome. As regards the last factor which could interfere with fat absorption, namely, alteration of the lacteal ducts, certainly this is the cause of very few cases of the disease. Because of the recent finding[25] that vitamin B complex and crude liver extracts exert a beneficial effect on patients with celiac syndrome, the opportunity is presented to study in more detail the nature of the disturbances in metabolism in this type of condition. However, it is apparent that the explanation of the faulty absorption of fat cannot be found with our present knowledge of the physiology of fat metabolism, and more studies of this condition are necessary.

SUMMARY

1. Ten children with the celiac syndrome were seen in the Department of Pediatrics at the University of Minnesota Hospitals from September, 1940, to August, 1942. Six of these patients died, in four of whom cystic fibrosis of the pancreas was demonstrated at autopsy. In the fifth and sixth patients autopsy was not performed, but the clinical symptoms and the laboratory findings suggested the same condition for at least one of them. Of the four children still living, one is considered to have a cystic fibrosis of the pancreas because of the abnormal response to the injection of secretin as well as the clinical nature and laboratory findings and family history. The other three living children with symptoms typical of the celiac syndrome left the hospital considerably improved. These patients are still under observation and the cause of their disturbance is still obscure.

2. In the eight patients in whom the serum lipids were studied, the values for the various fractions of the serum lipids (total fatty acids, acetone-soluble fatty acids, acetone-insoluble fatty acids, total cholesterol, cholesterol esters, and free cholesterol) were within the normal range of variability, except in one patient who had a low value for total cholesterol.

3. The iodine numbers of the fatty acids of all fractions of the lipid in these eight patients were abnormally low.

4. In five instances no increase in the serum lipids occurred following the ingestion of a fatty meal; in one patient there was a slight increase; in two the increase was normal. It happened that the latter two were considered unlikely to have a cystic fibrosis of the pancreas.

5. On two occasions no better absorption of fat was observed when the fatty meal consisted of a fat (corn oil) of a high degree of unsaturation.

6. The low degree of unsaturation of the serum fatty acids in the patients with celiac syndrome seems to be best explained on the basis of a deficient fat absorption. From these studies it is suggested that the human organism is unable to synthesize the more highly unsaturated fatty acids.

7. It appears that in patients with the celiac syndrome, the determination of the iodine numbers of the serum fatty acids might offer a means of ascertaining their ability to absorb fats. Since the steatorrhea, ordinarily present in patients with this condition is often lacking when the patient has been maintained on the usual relatively low fat diet, this might offer a relatively simple but helpful procedure in confirming the diagnosis and in evaluating clinical improvement in these patients.

8. The deficient fat absorption in the celiac syndrome seems to be difficult to explain with the present knowledge of the physiology of fat metabolism.

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THE EFFECT OF VITAMIN E ON REPRODUCTION IN DOGS ON MILK DIETS

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INTRODUCTION

PREVIOUS work has shown that dogs can be raised and maintained on mineralized raw milk for long periods of time (Potter, Elvehjem, and Hart[8]). When evaporated milk was fed under the same conditions, normal growth was obtained in the first generation, but all pups born to dogs fed evaporated milk died within five days after birth (Anderson, Elvehjem, and Gonce[2]). During the past three years studies have been continued to determine the cause of this difference in reproduction on the two types of milk. In this paper we wish to present evidence which indicates rather clearly that the difference is related to vitamin E. The data are limited, but due to the war emergency further experiments are impossible. Since the limiting effect of evaporated milk did not become evident until the dogs were carried through reproduction, it is doubtful that this observation can have any very extensive application in practical nutrition. However, as more is learned about vitamin E in infant nutrition, it may be important to recognize that evaporation tends to reduce the vitamin E content of milk.

EXPERIMENTAL

Weanling fox terrier female pups were fed diets of evaporated, aerated-fresh, and boiled milks. The evaporated milks were diluted 1:1 with water, and all milk diets were supplemented with 5 mg. of iron as the pyrophosphate, 1 mg. of copper as the sulfate, and 1 mg. of manganese as the chloride per dog per day. Vitamin D, 100 I.U., in the form of cod-liver oil was added to the ration of each dog daily. The milk diets were fed in earthenware crocks suspended from the sides of the cages to prevent contamination and waste. The animals were weighed weekly, the food intake was recorded daily during the growing period, and the skeletal development was observed.

Evaporated Milks.—Dog 1 has been maintained on mineralized evaporated milk for three years. During this time she has given birth to six

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litters of pups. The muscle dystrophy which occurred in the pups of the first two litters has been described by Anderson, Elvehjem, and Gonce.[1] Vitamin E at a low level was fed the dam during her third gestation. Anderson, Elvehjem, and Gonce[1] observed lesions on the legs, joints, lower jaw, and abdomen of the newborn pups of this litter. All six pups died within three days. Considerable free blood was found in the abdominal cavities, and three of the pups showed severe intracranial hemorrhages.

The presence of hemorrhagic areas suggested that some factor necessary for the strength of the blood vessels or for normal blood clotting might have been destroyed in the milk. The possibility existed that vitamin K was reduced during the processing of the milk. With this in mind Dog 1 was carried through a fourth gestation period and was given, in addition to 10 mg. of α-tocopherol acetate (Hoffmann-La Roche), 5 mg. of 2-methyl-1,4-naphthoquinone per week. The six pups of this litter died within three days after parturition. Autopsy showed all organs to be normal.

Inasmuch as the vitamin B_1 content of milk is relatively low in addition to the fact that the pups of litter 4 were very weak when born, the presence of a mild vitamin B_1 deficiency in the newborn pups was considered a possibility. Dog 1 was now carried through another gestation and lactation period with 4 mg. of vitamin B_1 per week in addition to 10 mg. of α-tocopherol acetate (Hoffmann-La Roche) and 5 mg. of 2-methyl-1,4-naphthoquinone. The fifth litter consisted of only one dog, dead at birth. No autopsy was obtained on this animal (Table I).

In order to be certain that these vitamin levels were not too high for favorable reproduction, the levels were lowered and Dog 1 was carried through another gestation. The vitamin supplements of 5 mg. α-tocopherol acetate (Hoffmann-La Roche), 3 mg. of 2-methyl-1,4-naphthoquinone, and 5 mg. of thiamine weekly, were fed orally in aliquot parts of the total dose during each week throughout pregnancy. The sixth litter consisted of four pups and all the animals died four days after parturition. On autopsy, the kidneys were large and pale, a condition which may be normal, as no positive controls were available. No hemorrhages were found in any of the pups. The stomach and intestines were empty in spite of the fact that the pups had been fed every two hours with the aid of a dropper and with milk obtained from the bitch. This method of feeding was necessary because the hind legs of the bitch were drawn up under her apparently from abdominal pain, and she exhibited a muscular twitching. When milked, the bitch would relax as if relieved from the pain.

To determine whether the above results on evaporated milk (brand A, neither sweetened nor irradiated) were typical, two young females were fed a second brand of evaporated milk (brand B, unsweetened but irradiated). Dog 33 was bred at 11 months of age and produced a litter of four pups, all of which died within three days. Autopsy revealed

TABLE I

SUMMARY OF REPRODUCTION RESULTS

DOG		TYPE OF MILK	SUPPLEMENTS/WK. IN ADDITION TO Fe, Cu, Mn AND COD LIVER OIL	GAIN IN WT. DURING GESTATION (GM.)	NUMBER OF PUPS IN LITTER	REMARKS
1	Litter 4	Evaporated	10 mg. α-tocopherol acetate 5 mg. 2-methyl-1,4-napthoquinone	1,350	6	All died within three days; no evidence of hemorrhage
	Litter 5	Evaporated	10 mg. α-tocopherol acetate 5 mg. 2 methyl-1,4-napthoquinone 4 mg. B_1	750	1	Dead at birth; dead too long for autopsy
	Litter 6	Evaporated	5 mg. α-tocopherol acetate 3 mg. 2-methyl-1,4-napthoquinone 5 mg. B_1	1,600	4	All dead within four days; no evidence of hemorrhage
33		Evaporated	None	1,000	4	All dead within three days; hemorrhages in cranial and visceral cavities
45	Litter 1	Evaporated	None	450	2	One dead in two days—small hemorrhages in lungs; second developed dystrophy in hind legs—died at 29 days but dead too long for autopsy
	Litter 2	Evaporated	40 mg. α-tocopherol	1,100	4	Normal pups; one developed muscle dystrophy in four weeks—placed on whole raw milk and completely recovered in three weeks; other pups after weaning grew satisfactorily on evaporated milk
36	Litter 1	Evaporated	None	600	3	One died shortly after birth—fractured skull; others died two days after parturition—severe cranial hemorrhages
	Litter 2	Evaporated	25 mg. α-tocopherol	1,300	4	All died shortly after birth; no abnormalities
37	Litter 1	Evaporated	None	725	2	One pup dead in two days—engorgement of cranial blood vessels but no hemorrhages; second pup dead in four days—severe cranial hemorrhages
	Litter 2	Evaporated	25 mg. α-tocopherol	1,100	4	One dead at birth; one dead in two days—normal on autopsy; other two dead in four days showing severe cranial hemorrhages
50		Aerated whole raw milk	None	550	2	First pup dead in five days, showing large hemorrhages on lungs; second pup showed a dystrophy syndrome in three weeks—lesions appeared on inner forelegs
39		Boiled whole milk with lactic acid		1,400	1	Normal growth past weaning

hemorrhages in the cranial and visceral cavities. All other organs were normal. The second, Dog 45, fed evaporated milk (brand B), was bred at 9 months of age and gave birth to two pups, one of which died two days after birth. On autopsy, the brain and viscera appeared normal, but there were small hemorrhages in the lungs. The second pup grew normally on the dam's milk but developed a severe muscle dystrophy a few days after birth. This pup lost control of his leg muscles and would collapse when placed on his feet. He died when 29 days old. No autopsy was performed.

Dog 45 was then carried through a second gestation and given 40 mg. of α-tocopherol (Merck) per week. Four normal pups were born in this litter. A month after birth one pup developed muscle dystrophy in its hind legs while still nursing from the dam. The pup was then placed on whole raw milk and in three weeeks muscle control of the hind legs had been regained. The other three pups of this litter were weaned and carried for four months on evaporated milk and they all appeared normal during this period.

To eliminate the possibility of some peculiarity in Dog 1 causing the death of her pups when on a diet of evaporated milk, two female litter mates, Dogs 36 and 37, were fed evaporated milk (brand A) supplemented with copper, iron, manganese, and cod-liver oil. Dog 36 had a litter of three pups, one of which died a few hours after birth. Autopsy revealed a fracture of the right frontal skull bone and the brain engorged with blood. The other two pups died the second day. Again there were large masses of blood between the hemispheres of the brain and severe hemorrhages could be seen. Dog 36 was now carried through a second gestation, during which time she received 25 mg. α-tocopherol (Merck) per week. All four pups of this litter died a few hours after birth. The pups were weak at birth, but autopsy revealed no abnormalities. The first litter from Dog 37 consisted of two pups, one of which died two days after parturition. Autopsy showed engorgement of the cranial vessels, but no actual hemorrhages were observed; the large intestine showed signs of severe hemorrhage. The second pup of this litter died four days after birth. Autopsy showed severe hemorrhages of the brain with a large mass of blood lying between the two hemispheres. Dog 37 was bred a second time and received 25 mg. of α-tocopherol (Merck) per week during gestation and lactation. Of the four pups in this litter, one was dead at birth, one died the second day and was found to be normal on autopsy. The remaining two pups died the fourth day and showed severe hemorrhages in the cranial cavity. The kidneys were slightly conjested and one pup exhibited severe hemorrhages in the large intestine.

Aerated Milk.—The above data indicate that the failure of female dogs to rear young when allowed to reproduce on a diet of evaporated milk is largely related to an insufficient intake of vitamin E. To produce a milk diet low in vitamin E, 10 mg. of iron as the chloride were

added to 1,500 c.c. of whole raw milk and the mixture aerated for thirty minutes. Dog 50 fed this milk through her growing period showed no deficiency symptoms. While still on this diet she was bred and gave birth to a litter of two pups, one of which died five days after parturition. Autopsy showed several large hemorrhages in the lungs. All other organs were normal. The second pup gained in weight but after three weeks developed a severe muscle dystrophy in the hind legs, similar to the symptoms of the pups of the first litter of Dog 45 fed evaporated milk. Lesions from 2 to 3 cm. in diameter were noticeable on the forelegs and around the hock and elbow. Two weeks later the dog's general condition seemed to improve, but it could walk only a short distance before the hind legs collapsed. It was thus possible to produce a condition similar to that observed with evaporated milk by aerating raw milk in the presence of iron.

Boiled Milk.—The qualities of canned milk and those of boiled acidified milk were also compared. Whole raw milk was boiled over an open flame for five minutes and then cooled. Immediately before feeding, 6 c.c. of U.S.P. lactic acid diluted 1:1 with water were stirred dropwise into each liter of milk. A litter mate of Dogs 36 and 37, Dog 39, was placed on a diet of the latter type of milk with daily supplements of iron, copper, manganese, and cod-liver oil. One pup was born to the dam on this diet. He grew well while suckling and after weaning at 6 weeks was placed on the same milk diet as the mother. This milk maintained him in good health and he grew well.

DISCUSSION

The data presented in this paper indicate that vitamin E is the principal factor concerned with the lack of proper development in young pups born of dogs on mineralized evaporated milk. Goettsch[3] found from 0.5 to 1.0 mg. of α-tocopherol given at the beginning of gestation would allow successful reproduction in the mouse. Gottlieb, Quackenbush, and Steenbock[5] have shown that satisfactory reproduction with the rat is possible on low fat diets when 0.85 mg. of dl-α-tocopherol was administered at the beginning of gestation. When a diet containing 20 per cent fat was used, Goettsch and Pappenheimer[4] obtained favorable reproduction in rats by giving 2.5 mg. of vitamin E at the beginning of gestation. Muscular dystrophy in the rabbit has been prevented by the daily supplement of 1 mg. of vitamin E per kilogram of body weight as reported by Mackenzie and McCollum.[7]

Although successful weaning of pups was not possible when dogs were fed 25 mg. of vitamin E per week during gestation, a normal litter was obtained when the level was raised to 40 mg. of vitamin E per week during the gestation period. Since 40 mg. per week is equivalent to approximately 1 mg. per kilogram of body weight for the dogs used, it is entirely possible that the negative results obtained upon feeding 25 mg. per animal per week were due to an insufficient intake of the

vitamin. It was clearly demonstrated by Waddell and Steenbock[9] that ferric iron destroys vitamin E. Although the mineral supplements were withheld from the dogs on the day that vitamin E was given, considerable destruction of the vitamin may still have taken place in the tract.

The bitch fed raw boiled milk, acidified with lactic acid and supplemented with iron, copper, manganese, and cod-liver oil, successfully raised the one pup of her litter. Boiling the milk did not seem to destroy the vitamin E of the milk inasmuch as the pup showed no evidence of dystrophy and it grew better on this diet than did the pups on any of the other milk diets.

Another significant observation is that, although Dog 1 was not able to raise normal young, she did produce six litters of pups. This indicates that evaporated milk is sufficient for the dog in every respect except for the extra requirements of the female dog during reproduction.

SUMMARY

1. Evaporated milk supplemented with iron, copper, manganese, and cod-liver oil supports normal growth in dogs but does not allow normal reproduction of the young by females on this diet.

2. The administration of from 5 to 25 mg. of α-tocopherol per week during the gestation period failed to correct the difficulty. Further addition of vitamin K and thiamine did not allow the young pups to survive.

3. When 40 mg. of α-tocopherol were fed weekly during the gestation period, normal reproduction occurred, although one of the four pups showed slight muscle dystrophy. The others were normal and after weaning grew satisfactorily on evaporated milk.

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DERMATOPATHIC LYMPHADENITIS IN INFANTILE ECZEMA

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LYMPHADENOPATHY has been commonly noted in patients with eczema. The enlargement of the nodes may be, and usually is, generalized but may be localized. All chains of lymph nodes may be involved, including the occipital, anterior and posterior cervical, axillary, epitrochlear, inguinal, and perhaps even mediastinal (Cases 1 and 2). This lymphadenopathy is dependent upon the concomitant and probably causative presence of a chronic skin eruption;[2] in our patients, infantile eczema.

The degree of enlargement is not necessarily related to the severity of the skin lesions but has been most marked in those of our patients who fall in the group described by Hill[1] under the title "Atopic Erythrodermia." In this group, the lymph nodes are visibly enlarged, frequently reaching the size of walnuts. Occasionally these latter suppurate and require surgical drainage. The size, however, is not dependent on the presence of infection superimposed on the eczema or on the severity of the eczema itself. In common with others, we have seen this adenopathy appear within a few weeks after the onset of the eczema, remain during spontaneous or induced remissions of the skin lesions, and disappear shortly after the eczema cleared up completely.

In the course of other investigations on infantile eczema we became interested in the associated lymphadenopathy but were unable to find any reference to the histologic appearance of the lymph nodes.

Accordingly, biopsy of cervical or inguinal lymph nodes was done in six instances, and this material forms the basis of this paper.

ABSTRACT OF CASES

CASE 1.—S. M. (J63966), a Negro female 3 years, 2 months of age, was admitted Dec. 9, 1942, for the second time because of generalized eczema. This had been present continuously since the age of 18 months and had responded intermittently to topical therapy. Moderate generalized lymphadenopathy had been noted. Eosinophilia varied from 2 to 9 per cent. An inguinal lymph node was removed Dec. 16, 1942. The basic structure of the node was well preserved. There were many lymphoid follicles with large, active germinal centers. Scattered through the lymph cords were small, discrete, and large confluent areas of paler staining larger cells which were presumably reticulum cells and which replaced the usual lymphoid tissue. Scattered through these areas were fairly abundant deposits of brown pigment. The sinuses were, in most instances, overrun by lymphoid cells and, as a rule, could not be distinguished, but where peripheral sinuses and

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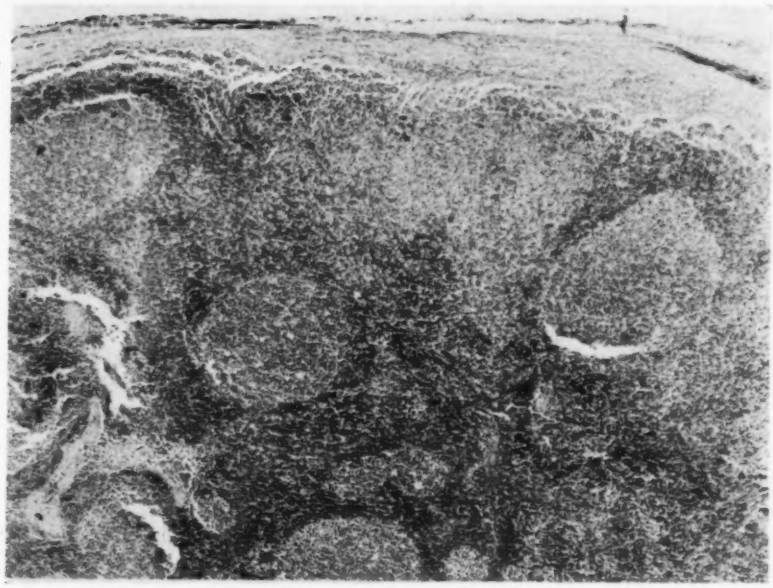

Fig. 1.—Peripheral portion of lymph node from Case 1. Germinal centers are conspicuous. In the center beneath the capsule is a clear area of reticulum cell proliferation shown in greater magnification in Fig. 2. The small black spots are deposits of melanin pigment. (×40.)

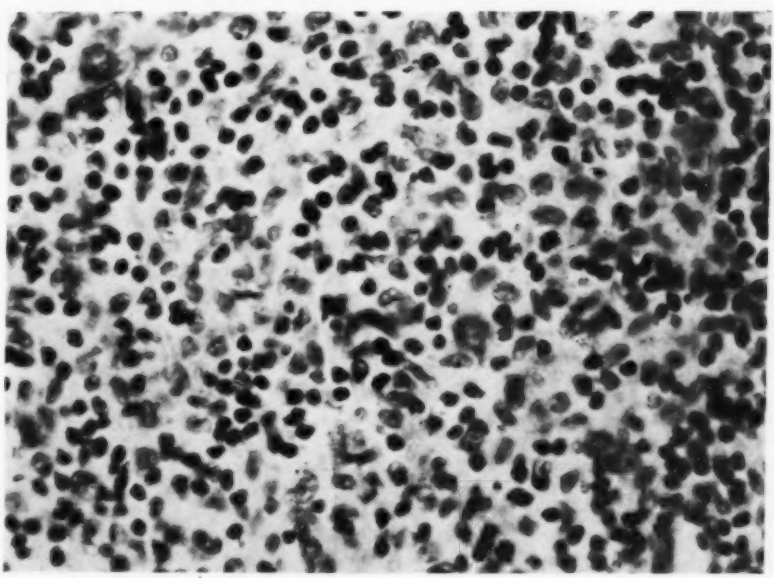

Fig. 2.—A higher magnification of the clear area in Fig. 1. Large clear reticulum cells are mingled with lymphocytes. (×1700.)

others could be differentiated, there was observed reticulum hyperplasia and a mixture of lymphocytes, plasma cells, and rare polymorphonuclears. The capsule of the node was intact. (Figs. 1 and 2.)

CASE 2.—F. P. (J65657), an 8-month-old white male, was admitted May 6, 1942, for the second time because of a severe generalized eczema, tremendous generalized lymphadenopathy, malnutrition, and frequent respiratory infections. The eczema was first noted at the age of 6 weeks and had resisted all forms of therapy over a long period of time. A soft tissue infiltration, retrolaryngeal and extending downward, was discovered by x-ray April 6, 1942, and numerous follow-up x-ray pictures indicated that the swelling was probably lymphoid in origin. Eosinophilia varied from 0 to 27 per cent. A cervical lymph node was removed May 19, 1942. Section showed preservation of the general structure of the lymph node. Lymph follicles were present at the periphery but did not have active centers. The principal change was the presence of small dense areas in the pulp, in which there were numerous reticulum cells or macrophages, some of which contained melanin pigment. Mingled with these cells were a few eosinophiles and plasma cells and an occasional leucocyte.

CASE 3.—R. G. (J65835), a 13-month-old white male, was admitted Oct. 16, 1942, for the fourth time because of severe generalized eczema, poor nutrition, generalized lymphadenopathy, and a chronic low-grade bronchopneumonia in the right upper lobe. Onset of the eczema was at 2 weeks of age. Enlargement of the hilar lymph nodes was discovered by x-ray at the age of 7 months. An abscess developed in the occipital nodes at 6 months of age and *Staphylococcus aureus* was cultured from the pus. Eosinophilia varied from 0 to 27 per cent. The patient's course was unsatisfactory over several months of therapy. An inguinal lymph node was removed Oct. 21, 1942. At the periphery of the node were normal-appearing lymph follicles with active germinal centers. In some parts of the cortex, between the follicles and in the medullary, portions were areas of reticulum cell hyperplasia. Here the reticulum cells assumed irregular shapes and occasionally contained melanin pigment. They were associated with lymphocytes and occasional plasma cells and leucocytes.

CASE 4.—V. T. (J63805), a 16-month-old white male, was admitted Dec. 2, 1942, for the fourth time because of severe generalized eczema, poor nutrition, generalized lymphadenopathy, and frequent, almost continuous, severe upper and lower respiratory infections. Eczema had first appeared at 2 months of age and generalized adenopathy shortly thereafter. An abscess developed in the occipital nodes at 5 months of age and *Streptococcus hemolyticus* was cultured from the pus. The patient's course was unsatisfactory over several months of therapy; his state of nutrition remained poor, eczema resisted treatment, and the degree of lymphadenopathy varied, frequently becoming worse when the severity of the eczema moderated. Eosinophilia varied from 0 to 31 per cent in the blood, frequently fluctuating from 5 to 25 per cent within forty-eight hours. An inguinal lymph node was removed Dec. 4, 1942. Sections showed small lymph nodes whose parenchyma showed preservation of the usual general structural features. They had thin intact capsules. They contained many medium-sized and large follicles, usually with large germinal centers, and thin to moderately thick rims of small lymphoid cells. The medullary cords showed multiple small, usually interconnected foci of reticulum cell hyperplasia with thin, cordlike or rounded residues of small lymphocytes intercalated. This change was quite extensive in some nodes and quite limited in extent in others so that sometimes only small portions of a

node were involved in this process. Through these areas there was a scattering of small amounts of brown pigment. The sinusoids were often overrun by lymphoid cells, but in a few foci most distinctly seen in the peripheral sinuses, they were dilated by a variety of cells. There was proliferation of reticulum, mobile macrophages, sometimes exhibiting phagocytosis, lymphocytes, and fewer plasma cells, and occasional polymorphonuclears.

CASE 5.—M. H. (J67649), an 11-month-old Negro male, was admitted Nov. 2, 1942, for the second time because of a generalized eczema and asthmatic bronchitis. The eczema had been present intermittently since the age of 3 months. Generalized lymphadenopathy was noted at the time of the first admission at the age of 6 months. The eczema had responded fairly well to treatment over a period of five months. Eosinophilia varied from 0 to 26 per cent. An inguinal lymph node was removed Nov. 21, 1942. The lymph follicles had active germinal centers. In the central portion of the node were scattered small areas of reticulum cells and macrophages, a considerable number of which contained brown pigment. Reticulum cells also appeared in some of the sinuses. Except for the pigment, the changes in these nodes were comparatively slight.

CASE 6.—G. N. (J72505), a 16-month-old Negro male, was admitted Dec. 9, 1942, for the first time because of a moderately severe generalized eczema present from the age of 5 months and resistant to all therapy. Generalized lymphadenopathy was noted on admission. A single blood count revealed no eosinophilia. An inguinal lymph node was removed Dec. 10, 1942. The intrinsic structure of the lymph nodes was preserved. There were many large follicles with active large germinal centers. The sinuses were overrun with lymphoid cells and usually could not be distinguished. Where the peripheral sinuses could be differentiated, these were seen to contain lymphocytes, a few plasma cells, and very rarely a polymorphonuclear. There was little or no hyperplasia of the sinus endothelium. Scattered through the medullary cords were a few small foci of hyperplasia of large, pale cells, presumably reticulum cells, with diminution of the numbers of lymphoid cells. Scattered through these areas was a minute amount of granular brown pigment.

DISCUSSION

Shortly after this study was undertaken, Hurwitt[2] reported identical changes in the lymph nodes removed from adult patients with nonspecific chronic skin disorders characterized by pruritis. To this condition he gave the name "dermatopathic lymphadenitis" and referred to articles in the French and Italian[3, 4] literature on the same subject.

Pautrier and Woringer[3] called these changes "lipomelanotic reticulosis," but, as noted by Hurwitt, this term is not accurate. Although many of the histiocytes present are lipophages and melanin is present, iron is also present and it is the replacement of the lymphatic tissue with proliferated reticulum cells, histiocytes, and fibroblasts that constitute the characteristic features of the pathologic changes of these nodes.

In his article Hurwitt described twelve cases chosen from a review of lymph nodes received by the pathology laboratory over a period of ten years. In common with our more severe cases, his patients had a chronic skin eruption with pruritus, lymphadenopathy, and a high

TABLE I

COMPLETE BLOOD COUNTS OF PATIENTS

NAME	DATE	FEBRILE	R.B.C	Hb.	W.B.C.	P	E	L	M	B	META-MYEL.	MYEL.
S. M.	1/ 8/42	No	3,930,000	11.0 Gm.	9,700	55	9	35	1			
F. P.	3/18/42	No	4,540,000	11.5 Gm.	13,000	43	25	25	6	1		
	4/13/42	No			8,700	30	2	66	1			1
R. G.	4/15/42	No	3,700,000	13.2 Gm.	10,600	19	12	64	3		1	1
	5/12/42	100.5° F.			47,000	33	20	41	4		2	
	5/18/42	No			5,400	16	22	52	10			
V. T.	5/27/42	No	4,010,000	11.8 Gm.	24,000	24	24	51		1		
	6/26/42	No			15,750	33	29	34	4			
M. H.	5/28/42	No	4,340,000	11.4 Gm.	17,600	43	10	44	3			
	6/10/42	No			10,200	35	22	43				
G. N.	12/10/42	No	4,650,000	9.3 Gm.	17,050	65	1	26	8			

P, Polymorphonuclear leucocytes.
E, Eosinophiles.
L, Lymphocytes.
M, Monocytes.
B, Basophiles.
Metamyel., Metamyelocytes.
Myel., Neutrophilic myelocytes.

eosinophile count in the blood. His patients, however, were all males and varied in age from 36 to 78 years.

Duany[5] reported the case of a 2-year-old child with chronic eczema and generalized adenopathy, including hilar nodes, with leucocytosis (16,000 to 35,000) and eosinophilia (12 to 27 per cent). Biopsy of the node showed a thin capsule, hyperplasia of the reticulum; infiltration with eosinophiles, lymphocytes, lymphoblasts; histiocytic cells with hemosiderin. Pathologically he considered the changes to be very similar to those of Hodgkin's disease.

Reports of the same or similar cases in adults by Pautrier and Woringer,[3, 4] Pinetti,[6] Goedhart,[7] Soloff,[8] Nudana,[9] Cannon,[10] and Combes and Bluefarb[11] have been discussed by Hurwitt.

The six patients studied in this series present certain features in common. The eczema had been chronic, usually refractory to therapy; a high eosinophile count was frequently present, as well as a leucocytosis (Table I), especially during the acute phase of respiratory infections; lymphadenopathy had been generalized, frequently severe, and made its appearance shortly after the eczema appeared; the lymphadenopathy was thought originally to be secondary to infection of the skin, although a careful perusal of the history of these patients showed this to be a fallacy; the patients were all young, the oldest being only 3 years and 2 months and the remainder varying from 8 to 16 months of age; findings characteristic of dermatopathic lymphadenitis as described by Hurwitt are present in the biopsied lymph nodes of all.

In the more severe cases the degree and generalized nature of the adenopathy, including even mediastinal nodes in some, in association with the poor nutritional state of the infant and frequently high leucocyte counts, suggests clinically a blood dyscrasia. Hurwitt records that in some of his cases the microscopic appearance has a slight resemblance to Hodgkin's disease. In this connection, the case of Fraser[12] should be noted, in which the resemblance to a blood dyscrasia was accentuated by the presence of a leucemoid blood picture.

The benign nature of this condition, however, is evident to those who have observed these patients over a period of years. The conclusions of the various authors who have studied this condition have been in agreement with our findings and those of Hurwitt; namely, that "the adenopathy was of a benign reactive nature in response to the skin disease as an irritant."

CONCLUSION

1. The pathologic changes in the enlarged lymph nodes found in patients with infantile eczema are the same as those described by Hurwitt as "dermatopathic lymphadenitis."

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A DOUBLE OVA PREGNANCY IN WHICH THE RH+ TWIN DEVELOPED ERYTHROBLASTOSIS

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THE relation of the Rh factor to erythroblastosis has been fairly well established in the few years that have elapsed since its discovery. The case to be presented in this report, however, together with one which was recently observed by Kariher,[1] gives more definite evidence of this relationship than has been previously available.

On May 14, 1943, twins were born at the Chicago Lying-In Hospital to a normal 32-year-old woman who had had one uneventful pregnancy nine years previously. The twins were both male, and placentas and amniotic sacs were separate. One infant survived and was entirely normal; the other died of erythroblastosis on the second day of life. The mother has shown no anti-Rh agglutinins but is OMN Rh−; the father, ON Rh+; the 9-year-old daughter, O Rh+; the living infant, OMN Rh−; the dead infant, OMN Rh+. This seems proof that an Rh+ infant could develop erythroblastosis in an environment which would leave an Rh− infant unaffected.

The case reported by Kariher[1] is almost identical. Double ova male twins were delivered in April, 1943. One was normal; the other died of erythroblastosis on the second day of life. The parents and infants were all group A; the mother and the normal twin, Rh−, the father and the affected twin, Rh+. The mother had had one previous pregnancy. The Rh of this child is not stated.

Relatively few twins suffering from erythroblastosis have been reported since this condition has been recognized as a definite pathologic entity, and, in the majority, both twins were affected. The older literature contains occasional cases in which one twin was edematous and the other was not, but it is known that universal edema may occur in the absence of erythroblastosis,[2] and there is little evidence to support the conclusion that erythroblastosis was the cause of the edema in most of these cases. Maharik,[3] in 1940, reported the birth of one normal and one edematous twin, the latter exhibiting a profound erythroblastic anemia which was diagnosed as erythroblastosis. He states that an examination of the placenta proved they were single ovum twins, but at the present time few geneticists will agree that the placenta alone is a sufficient basis for such a statement. It would seem probable that either the diagnosis of erythroblastosis or of single ovum twinning was in error.

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Mellinghof and Randerath,[4] in 1940, reported a pair of double ova twins with both infants dying of icterus gravis. These authors state that in 1938 Pache found twenty-three instances of twin pregnancies in which one or both infants were stated to have erythroblastosis. In eighteen pairs of double ova twins both had the disease. Oddly enough, in the five reported as single ovum twins the diagnosis of erythroblastosis was made on only one infant of each pair. Mellinghof and Randerath conclude, however, that the disease was not excluded in the twin reported as normal and that both were probably affected, the condition being more severe in one than in the other.

Since Rh determinations have been possible, one pair of twins, both of whom died of erythroblastosis, was born at the Chicago Lying-In Hospital. Both twins and the father were Rh+; the mother, Rh–. One other pair of twins, both of whom suffered from erythroblastosis, but who survived, has been observed by Dr. I. Davidsohn.[5] Here, also, both twins and the father were Rh+; the mother, Rh–.

In the case described in this report, the existence of the disease in only one of two infants exposed to the same intrauterine environment would seem to indicate that some intrinsic difference in the fetuses was most probably responsible for its occurrence in one and not in the other. The present theory of the etiology of erythroblastosis places the Rh factor as the most common causative agent of this disease. Although it appears that A or B agglutinogens or possibly other unknown agents may occasionally produce the same result, the great majority of cases are dependent on the Rh factor, and only this will be discussed here. If the Rh factor is the agent responsible for the development of erythroblastosis, the disease is limited to those fetuses that are Rh+. In other words, in order for a fetus to be affected by anti-Rh agglutinins coming to it through the placenta from the mother, it must possess an antigen (Rh+ cells) which will complete the antigen-antibody reaction. If the fetal cells do not contain the antigen, i.e., if they are Rh–, the agglutinins which reach the fetus will do no harm inasmuch as there is no antigen present with which they can react, and the cells cannot be agglutinated.

It requires an Rh+ fetus and the escape of fetal cells from the placenta into the maternal circulation (or the introduction of Rh+ cells into the maternal circulation by transfusion) to produce anti-Rh agglutinins in the mother. From a study of the reproductive histories of many women giving birth to infants with erythroblastosis, it appears that the antibodies are rarely developed in sufficient numbers during the pregnancy in which initial sensitization occurs to produce a fatal form of erythroblastosis in the fetus carried during that pregnancy. Subsequent pregnancies, however, seem to stimulate further production of antibodies, even though the specific antigenic cause may be lacking. I believe that a form of anamnestic reaction exists in relation to pregnancy, so that every time a woman again becomes pregnant after she

has once developed anti-Rh agglutinins, new agglutinins are produced in the old anti-Rh pattern, even though no more antigen, in the form of Rh+ fetal cells, enters her circulation. It has been presumed by some investigators that a break in the fetal circulation, or an abnormal permeability of the fetal vessels, must exist in every pregnancy during which erythroblastosis occurs. On this basis Burnham[6] has suggested giving large amounts of vitamin C during pregnancy to women who are known to have previously given birth to infants with erythroblastosis. He believes this might prevent injury to placental blood vessels and thus keep the cells from escaping. Haldane[7] has postulated the existence of a specific gene causing abnormal permeability of the placenta and states that the limitation of erythroblastosis from approximately 1 in 10 pregnancies where an Rh– woman carries an Rh+ fetus and where the disease could occur to the 1 in 200* in which it is actually observed is because of the infrequent occurrence of the gene causing abnormal permeability.

The simplest and only really adequate explanation of the great frequency with which erythroblastosis is repeated in subsequent pregnancies lies in the fact that something probably happens to the mother during one pregnancy which is permanent and which affects all the fetuses of subsequent conceptions. If this is true, and anti-Rh agglutinins persist even though nondemonstrable by any laboratory tests, the only fetuses which escape will be those that are Rh– and who cannot react to the maternal antibodies.

It has been calculated that in the random population 47.7 per cent of all individuals are heterozygous for the Rh factor and 36.9 per cent are homozygous, although both appear Rh+ since the Rh+ character is dominant over the Rh–. Therefore, about 50 per cent of the Rh– women married to Rh+ men will have only Rh+ children, while the others would be expected to bear approximately one-half Rh+ and one-half Rh– children. In the first group all children born after sensitization of the mother would be expected to develop erythroblastosis, while in the second group one-half of the children in subsequent pregnancies would be expected to escape.

Of over fifty women in my series who have given birth to infants dying of erythroblastosis, twenty-two have subsequently delivered thirty-seven infants and none have escaped the disease. Only four have survived. Other investigators, however, have reported the occasional birth of normal children. Javert states that in thirty-six pregnancies among women who had previously given birth to an infant with erythroblastosis eight were normal infants.

The constant repetition of the disease in the patients in my series has brought forth the speculation that the condition might probably be limited to the homozygous Rh+ state in the father or that in some way

*This is a figure arrived at by Haldane as a result of his belief that many cases of erythroblastosis are undiagnosed. In my opinion it is unjustifiably high.

Rh– fetuses might become affected. The latter contention does not seem feasible in view of the fact that almost without exception the examined fetuses have been Rh+. The case reported here seems to give definite proof that the condition cannot be limited to those instances where the father is homozygous, inasmuch as this father must have been heterozygous in order to have had one Rh+ and one Rh– offspring. It is conceivable that the twins had different fathers, but the contended father cannot be excluded on the basis of any known test. The identical nature of the case reported by Kariher makes it almost outside the realm of possibility that each of both pairs of twins had different fathers. It must be concluded that when the father is heterozygous for the Rh factor, anti-Rh agglutinins circulating in the maternal blood will produce the disease in an Rh+ fetus and leave one who is Rh– free.

The case history of the twins delivered at the Chicago Lying-In Hospital is as follows:

Mrs. A. B., 32 years of age, para i, gravida ii, was admitted to the hospital in the first stage of labor two weeks prior to the expected date of confinement. She had had one previous pregnancy at the age of 23 years which ended in the birth of a normal female child who is now alive and well. The present pregnancy had been uneventful. Male twins were delivered, each in a breech position, after an uneventful labor lasting one hour. The placentas and amniotic sacs were entirely separate. Twin II weighed 2,815 Gm. He was sent to the regular nursery, gained normally, and was discharged in good condition on the eleventh day of life.

Twin I weighed 2,125 Gm. and was consequently admitted to the premature nursery. He developed a moderate jaundice within twelve hours of birth. The jaundice increased, and early on the fourth day evidence of mild cerebral irritation was present. A blood smear at this time showed no nucleated red blood cells and a normal differential count (polymorphonuclear leucocytes, 60; lymphocytes, 22; monocytes, 10; eosinophiles, 4; metamyelocytes, 2; stab cells, 2). Twelve hours later another smear showed the leucocytes apparently much reduced in number and 16 nucleated red blood cells per 100 leucocytes. The total white count was 1,600; red blood cells, 2,300,000; hemoglobin, 10.5 Gm. The infant was given 30 c.c. of blood intravenously but died a few hours later.

Autopsy examination disclosed a male infant weighing 1,980 Gm., measuring 46 cm. in length, and exhibiting an extreme generalized icterus. The basal nuclei in the brain and all of the tissues on the interior of the body were a deep, bright yellow. There was no visible edema and no fluid in any body cavity. All organs appeared normal with the exception of the spleen, which weighed 13 Gm., a weight slightly more than twice the average for this total body weight. The other organ weights in grams were as follows: heart, 16.0; left lung, 22; right lung, 28; liver, 90; pancreas, 2.5; each kidney, 10; each adrenal gland, 3.8. Blood smears taken at autopsy showed 112 red blood cells with nuclei in various stages of development per 100 leucocytes. All polymorphonuclear leucocytes were slightly immature. Post-mortem blood cultures were negative.

Histologic examination of the organs revealed deposits of golden brown pigment in interstitial spaces and in macrophages throughout all organs. It was also present in hepatic cells and reticuloendothelial cells of the liver and in the cells of the kidney tubules. Much pigment was present in macrophages and in glial cell and intercellular spaces in the region of the basal nuclei in the brain.

The liver showed extreme activity of the reticuloendothelial system; the sinusoids contained large numbers of free endothelial cells and a moderate number of cells resembling hemocytoblasts. A few hemocytoblasts were present in the capillaries of the kidney glomeruli, in the capillaries in the lungs, and in the spleen.

Extramedullary erythropoiesis, which is usually very marked in erythroblastosis, was lacking except for a mild degree in the liver and spleen. This is not a surprising finding, however, in view of the fact that immature cells do not appear to have been present in the blood of this infant until a very short time before death. It is regrettable that earlier blood studies were not made, for, although the infant doubtless had an anemia at birth, the extreme jaundice which was present at the time of death would indicate that blood cell destruction had been actively progressing during the infant's brief lifetime. Before birth, the hematopoietic system did not seem to have been sufficiently affected to have responded with the production of ectopic areas of erythropoiesis; some time after birth, an agent, doubtless having its origin in utero, began to act and finally caused the death of the infant. The escape of immature red blood cells into the peripheral circulation seems to have been a terminal attempt on the part of the body to compensate for the small number of mature erythrocytes which were present in the circulating blood.

SUMMARY

Twins, one of whom died of erythroblastosis while the other remained normal, are reported. The affected twin and the father were Rh+; the normal twin and the mother were Rh–. It is contended that the father was heterozygous for the Rh factor and that two ova were fertilized, one by a sperm carrying an Rh+ gene and the other by a sperm carrying an Rh– gene. The Rh– mother had been sensitized to the Rh factor either in the previous pregnancy, when an Rh+ fetus had been carried, or possibly during the course of this pregnancy by the Rh+ twin. The antibodies produced in the mother passed through the placentas of both fetuses but affected only the one which was Rh+. The cells of the Rh+ fetus contained the Rh antigen and could be agglutinated by the Rh antibodies; the cells of the Rh– fetus contained no antigen and therefore could not be agglutinated. The fetus whose cells were agglutinated developed erythroblastosis; the one whose cells were not agglutinated remained well.

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AN EPIDEMIC OF COMMON INFECTIOUS JAUNDICE

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LAPEER, MICH.

AN EPIDEMIC of common infectious jaundice totaling 100 cases was observed in a period of thirteen months at the Lapeer State Home and Training School, an institution for the care of the feeble-minded. There had been no jaundice among the new patients at the institution before the epidemic began, and no more than an ordinary number of cases were found among those who came in during the epidemic period.

The institution is located a mile from the town of Lapeer, Mich., a rural community of 5,000 people. It is distinctly separated from the town, having its own electric power, water supply, and sewage disposal plants. The patient population at the time of the study was 4,200, housed in cottage-type buildings, between 100 and 125 persons living in each cottage. Patients are placed in buildings according to their intellectual and age levels with resulting significant social differences from one building to another. The intellectual groupings are idiot, imbecile, and moron. Patients in the idiot group frequently are untidy, spend a good deal of time on the floor, and have a persistent habit of putting their fingers in their mouths. They remain in the same room in the same building day in and day out. Among the moron group most patients spend at least a part of each day away from their home building. They are able to follow simple rules of personal hygiene. For very obvious reasons their physical environment is markedly more sanitary than that of the idiot group. Age distribution, according to building, is less rigidly adhered to than is intellectual level, but within buildings persons are arranged so that in general the age groupings have significance in the way that will be described below.

For several months before the jaundice began, in May, 1939, there had been in one building an epidemic of bacillary dysentery caused by the Hiss-Y organism. This was traced to a contaminated water supply and to the presence of carriers. The dysentery was overcome in June, 1939, by elimination of the impure water. It is doubtful if any relationship existed between the two epidemics but their chronological coincidence is noted.

There seemed to be a relationship between the incidence of the disease and the social setting of the patients. A proportionately larger number of cases appeared among the idiot group than among the morons (Figs. 1 and 2). Age groups showed definite differences. The highest incidence was in the age group 10 to 14 years, while the groups 15 to 19 and 20 to 24 showed the next highest in that order (Figs. 3 and 4). Percentages of the total population in each age group developing jaundice

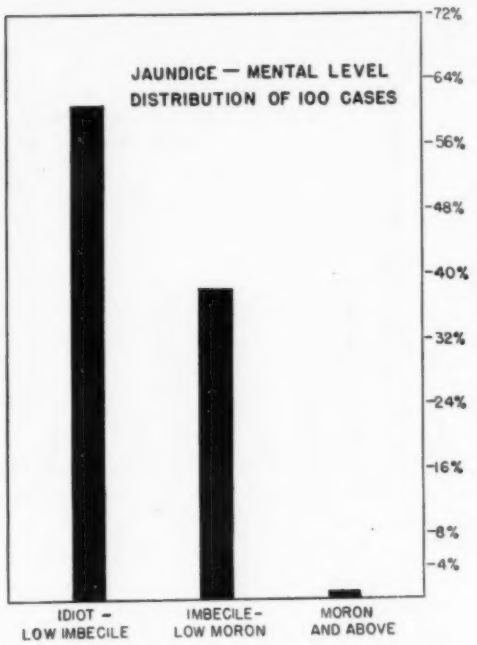
JAUNDICE — MENTAL LEVEL
DISTRIBUTION OF 100 CASES
72%
64%
56%
48%
40%
32%
24%
16%
8%
4%
IDIOT - LOW IMBECILE
IMBECILE - LOW MORON
MORON AND ABOVE

Fig. 1.

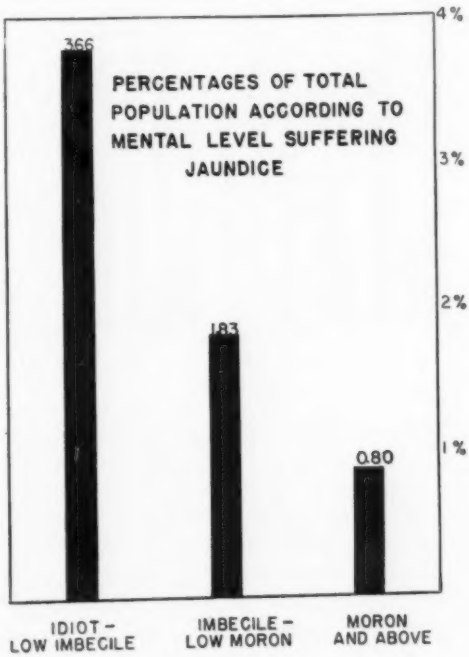
4%
3%
2%
1%
366
PERCENTAGES OF TOTAL
POPULATION ACCORDING TO
MENTAL LEVEL SUFFERING
JAUNDICE
1.83
0.80
IDIOT - LOW IMBECILE
IMBECILE - LOW MORON
MORON AND ABOVE

Fig. 2.

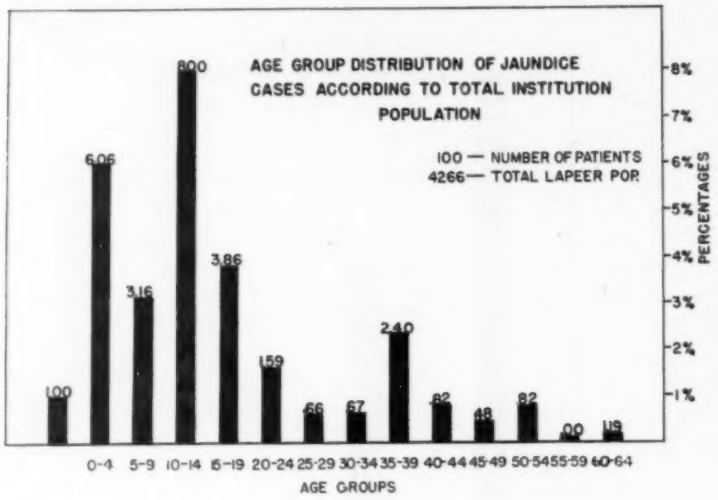

Fig. 3.

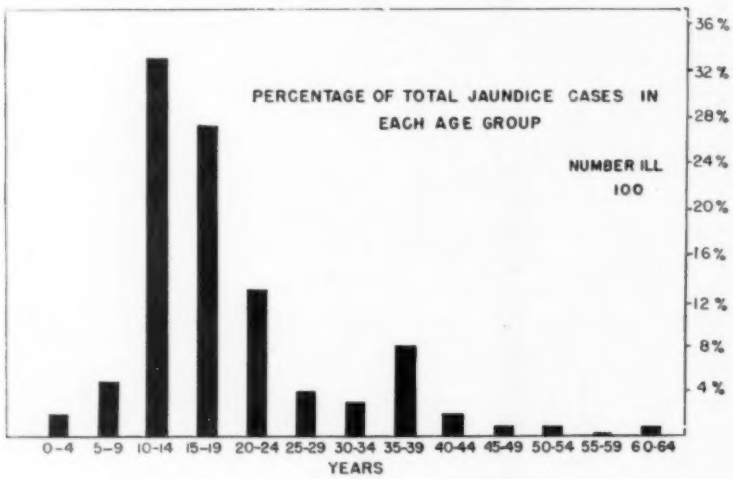

Fig. 4.

showed approximately the same graphic picture except that there was a rise in the number of cases in the age group 0 to 4 years. The percentage comparison probably is more accurate for estimating incidence in relation to age groups since the population was stable and confined to a definite area during the entire period of study.

There was a significant difference in the percentages ill between cottages with active population (Fig. 5). There were approximately 1,000 individuals living in each of the two groups of buildings compared.

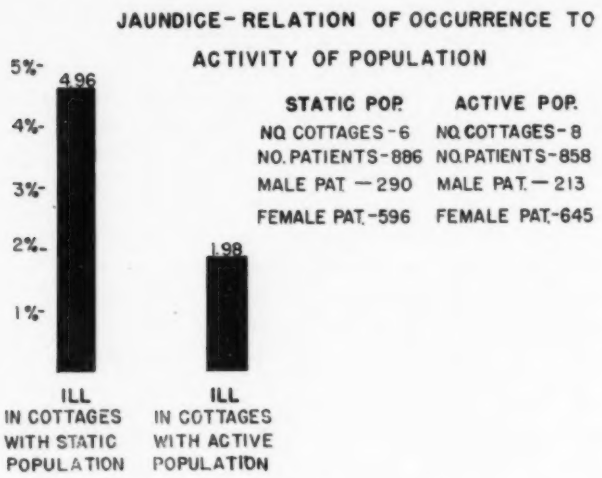

Fig. 5.

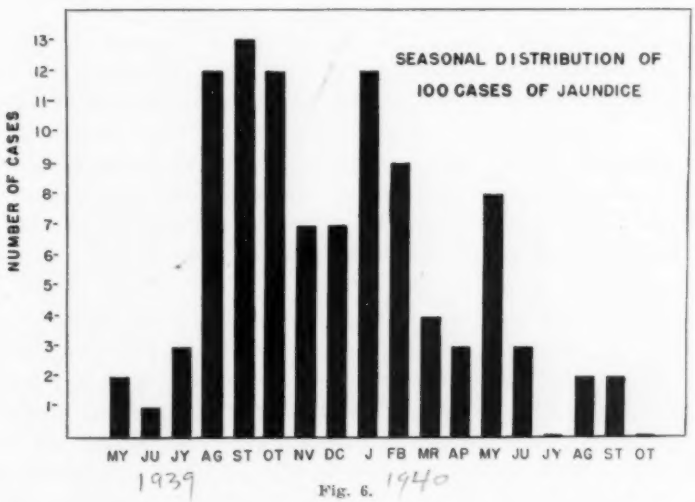

Fig. 6.

Approximately five inactive persons were ill to every one active individual who suffered jaundice.

A definite periodicity in the occurrence of cases in the general epidemic was noted (Fig. 6). This same periodicity was shown in occurrence by buildings (Fig. 7). In addition, the epidemic did not proceed in orderly fashion but jumped about indiscriminately. Neither was the progress in individual cottages even. In some buildings the span of the epidemic was short in time, in others it was long. In the cottages where the epidemic started, for instance, the first case was reported in May,

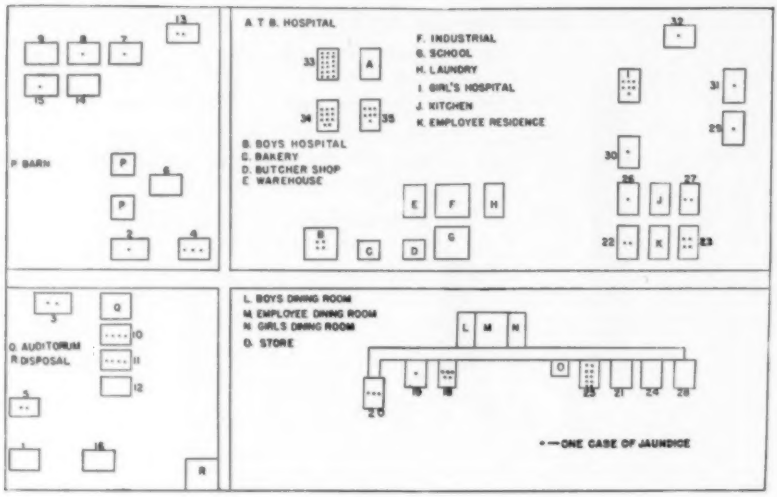

Fig. 7.

1939. Yet, between July, 1939, and October, 1940, no cases were reported. This building belonged to the static population group and there was little contact among the residents with other persons in the institution.

It appeared that the disease was communicable, and it seemed to have been a contact infection. Two factors contraindicate droplet infection: one, the lower incidence among the more active population and, the other, the highest incidence among custodial patients, many of whom were crippled and untidy.

Some of the epidemiologic features are as follows: The epidemic was in a rural setting in a temperate zone. There was a marked seasonal incidence in that approximately 65 per cent of the cases appeared in the fall and winter months. The cases occurred in groups spaced at an interval of about one month. Recurrence of the disease was noted in two instances, when one person became jaundiced one month after the initial attack and the other, three months after the initial attack.

All but one patient recovered. This patient did not appear acutely ill; her temperature was only slightly elevated, and her white blood count was 10,000. Characteristic signs as well as the course of her illness were not those of acute yellow atrophy of the liver. Since an autopsy was unobtainable in this instance, pathology cannot be described for any case in the epidemic.

The clinical features were remarkably constant. The disease was almost always mild. Typically there was a prodromal stage of malaise which extended from one to ten days before the appearance of jaundice.

The intensity and duration of the jaundice varied. It was difficult in some instances to detect icterus in the skin, although the sclera showed pigmentation for prolonged periods.

The usual history given by building supervisors included listlessness and indifference to play for a varying period of time, headache, and a definite anorexia. Occasionally vomiting occurred. Diarrhea appeared, during the first stages of the epidemic, with more than incidental frequency, yet constipation seemed to be a more characteristic symptom. Within a few days the sclera would become yellow. From a few hours to a day after yellow sclera became apparent, the patient developed an icteric tint and within twenty-four to forty-eight hours the entire body would be yellow. The usual color of the jaundice was more golden yellow than greenish yellow. Often the urine appeared dark before the onset of the jaundice. At the time of the jaundice the stools became clay colored, remaining so for varying lengths of time.

The physical findings at the time of hospital admission (when the sclera had become yellow) showed mild illness. There was little evidence that the skin was itchy. In a few cases, especially early in the epidemic, the liver was palpated one to two fingerbreadths below the costal margin. Almost invariably epigastric tenderness was present. Urine was dark and stools were clay colored. Sixty-six per cent of the patients showed some fever, seldom over 100° F. Four patients showed fever of 102° F. and one patient, 105° F. Among 62 per cent of the patients the jaundice persisted from one to ten days; among the rest it lasted from eleven to fifty-four days. There were two patients who maintained high temperatures and intense jaundice, one for twenty-eight days and the other for fifty-four days. Both of them were in the idiot classification and came from the cottage which showed the highest incidence per population.

Blood counts were made on twenty patients; all but five showed a definite leucopenia. In no instance was there a leucocytosis. No relative or absolute lymphocytosis was noted except in one patient who showed 88 lymphocytes and 9 monocytes, with a total white blood count of 6,800. The lowest count noted was 4,000, which occurred in an adult 28 years of age. The patient who died had a white blood count of 9,000 with a differential of polymorphonuclears, 63 per cent, and lymphocytes, 27 per cent.

Urine, dark in color, at some periods showed urobilin, usually shortly after the onset of the jaundice. Acetone was not noticed except in one patient suffering from diabetic acidosis. Albumin was not a characteristic finding in the urine although it occasionally occurred. Cultures of the stools showed no members of the typhoid, paratyphoid, or dysentery group to be present. *Staphylococcus aureus* was recovered from the stools of two patients, but this was not thought to be significant. Biliary drainage was done on six patients during the height of the jaundice by stimulation with magnesium sulfate and olive oil. No epithelial cells

or calcium oxalate crystals were noted in the bile, but cholesterol crystals were present. Cultures of bile showed contamination with yeast in two cases. Four others showed *Staph. aureus*. Galactose tolerance tests were done on ten patients. All showed decreased tolerance to galactose and presumably impairment of liver function. Four patients were rechecked after recovery for liver function by the galactose tolerance test. All these still showed some impairment of liver function. There were no galactose tolerance tests on patients before they developed jaundice, but it seems unlikely that all could have shown impairment of liver function. One patient, seen because of recurrent jaundice, gave an initial diagnostic impression of common infectious jaundice, but a complete work-up showed that he had pernicious anemia. His galactose tolerance test showed no impairment of liver function, although he had clinical jaundice. Two other patients who had jaundice and were shown to have microcytic hypochromic anemia had galactose tolerance tests. There was no impairment of liver function as measured by this test. Fragility tests on several patients showed no change in the degree of hemolysis of red cells as compared to a control. Urine from several patients was sent to Dr. Larsen, U. S. Public Health Service, and Leptospira were never demonstrated after inoculation into a guinea pig.

Approximately fifty patients receiving arsenicals in the treatment of syphilis were exposed to this outbreak, but only one developed jaundice. One patient mentioned previously, suffering diabetes, developed the disease. Rather severe and protracted diabetic acidosis occurred and was difficult to control. Six patients developed jaundice in association with upper respiratory infections or sore throats.

Several forms of treatment were tried. Most frequently a high carbohydrate diet and magnesium sulfate were prescribed. These drugs usually were given at the height of the jaundice for periods varying from two to seven days. Ten patients were placed upon a diet consisting of eight ounces of an equal mixture of milk and 40 per cent cream every five hours. With this they received luminal, desicol, and tincture of belladonna. No apparent difference of tolerance to diet was noted between the patients in this group and those given a high carbohydrate diet. Patients were usually kept in bed until their jaundice disappeared. There were no age differences in the length of the period of convalescence. Some individuals complained of fatigue, malaise, and anorexia for periods up to three weeks after the onset of the jaundice.

REVIEW OF LITERATURE

Cullinan,[1] in reviewing the epidemiology of jaundice, says the disease is not spread by water, milk, or food but from person to person and the contact is nearly always close. Reports of two epidemics have inferred that the virus might lodge in a contaminated water supply. The dormitory and family spread suggests a droplet infection. Bashford,[2] in 1934, reporting an epidemic in the London General Post Office, found cases in

only one section of the post office. The attack rate was fairly high. He felt contact to be only casual. All authors are doubtful about the mode of conveyance, but they agree in thinking it is a contagious disease, and most believe it is the result of contact and of a droplet infection. Most discussants note unexplained gaps which may be explained by carriers. Then, too, many cases are so mild as to be missed. The incubation period is long, which may explain why the disease is endemic in certain areas.

Marked incidence has been noted with epidemics usually having their peak in the winter months (Cullinan,[1] Blumer,[3] and Cockayne[4]). Cases may occur in the spring, fall, and summer. Blumer[3] tabulated the percentages by season in America as follows: 72 per cent fall and winter; 12 per cent began in summer and continued to fall; 6 per cent in spring.

There has been a remarkable uniformity of opinion as to the age groups affected. Pickles[5] suggests that the disease attacks all ages indiscriminately, but many authors feel that adults have more immunity than children, most cases falling into the group of children and adolescents. Cockayne,[4] Cullinan,[1] and Blumer[3] remark upon this also. In 70 per cent of the fifty epidemics analyzed by Blumer,[3] children and young adults only were attacked.

The literature reveals that there may be some significant difference of incidence, dependent upon whether the environment be urban or rural. Many of the epidemics reported have occurred in isolated rural areas, such as the recent occurrence in a small mining town in the United States.[6] A review of many epidemics shows that there is probably no significant increase of cases in rural areas.

Previous attacks apparently do not make patients more susceptible. Neither does a previous attack seem to confer a permanent immunity. Infectious jaundice is not associated with other diseases to any significant degree. There is a possibility of a relationship between common infectious jaundice and jaundice following injections of arsphenamine. An interesting feature in reviewing jaundice patients receiving arsphenamine is that a large number of cases of so-called postsalvarsan jaundice occur in epidemics irrespective of the preparation of the drug or the way in which it is given. Jaundice following arsphenamine is frequently delayed. Wile and Sams[7] found that two-thirds of their cases occurred at an average interval of eighty days after the last dose had been given. This leads one to the thought that postarsphenamine jaundice may be identical with common infectious jaundice. Greater severity in clinical symptoms suggested syphilis and salvarsan as agents which rendered a liver more susceptible to the disease.

In association with other diseases, sore throat is mentioned in several epidemics. Cockayne,[4] Glover and Wilson,[8] and Cullinan,[1] in reviewing the epidemiology, thought that sore throats were incidental and not really part of the clinical picture of the disease.

In an epidemic reported in Detroit,[9] contacts in some instances developed a typical prodrome, some darkening of the urine and changes in color of the stool, without jaundice. It is probable that this variation in the behavior of the disease resulted in the missing of some atypical secondary cases. Most English authors reporting epidemics have noted the same variation of the disease and for this reason postulated the possibility of carriers. Cullinan,[1] in his review of the etiology of common jaundice, feels that this is an important factor in keeping the epidemic going.

Climate seems to have little effect, as epidemics have been reported in all parts of the world. Most detailed reports of the disease have come from the temperate zones. Blumer[3] reported records of the disease throughout the United States. It is a widespread disorder, according to Cullinan,[1] occurring in all parts of England. It is not entirely a disease of temperate zones, although many of the reports are from countries in this area of the world. An epidemic has been reported in Turkey.

The course of disease, especially the mode of onset, has been variable, not only in different epidemics, but also among patients in a single epidemic. This has been noted by practically every author reporting epidemics of infectious jaundice. Usually the onset is fairly sudden with marked gastrointestinal symptoms, nausea, vomiting, constipation, severe headache, pain in the back and limbs, epigastric pain, and fever. The fever usually is not very high. The period of febrile gastrointestinal manifestation usually quiets down on the fifth day. Blumer[3] described this as presumably the incubation period, but most authors feel this is the invasive period. There is marked variation in the intensity and duration of the jaundice. In Blumer's review the jaundice was reported to persist usually for a week to ten days, although it sometimes disappeared after a few hours or, in some instances, persisted for six weeks or longer. Itching sometimes occurred. The characteristic color, if there is any, is orange-yellow. Molner and Meyer,[9] in reporting the jaundice epidemic in Detroit, state, from an analysis of 200 cases, the mean duration of jaundice to be 10.5 days and the median, seven days. About twenty-eight of their patients were jaundiced over fifteen days.

The causative organism of common infectious jaundice is not known. A few authors have suggested that the etiology may be related to the typhoid-dysentery group. Klemperer[10] suggests that the *Bacillus paratyphosis* B may be of etiologic significance. In an epidemic reported by Yenikomshian and Dennis[11] in the Lebanese Republic, sera examined in affected patients for the presence of agglutinins against *Eberthella typhosus*, salmonellae, paratyphosus, and also against a certain gram-negative lactose-fermenting bacilli, which were isolated from the village water supply in the particular epidemic, showed inconclusive results.

No reviews of this disease suggest that the etiology is related to the presence of microorganisms or virus in the stools. Apparently the

etiologic agent gains entrance to the blood stream and lodges in the liver. There have been few reports of stool cultures, which is not unusual, as constipation is more common than diarrhea in this disease.

Numerous attempts have been made to transmit the infecting agent to animals.[12] Material, including whole blood, blood serum, nasal washings, feces, and urine, has been obtained from cases during epidemics. Material has been obtained from patients in the preicteric stage or within twenty-four hours after the onset of jaundice. Efforts to infect monkeys, hedgehogs, dogs, cats, ferrets, rabbits, guinea pigs, field mice, rats, fowl, and pigeons have been unsuccessful. Material has been given intraperitoneally, subcutaneously, and intracerebrally by nasal instillation and by feeding. All efforts to produce a disease resembling infectious hepatitis have proved negative, nor has any greater success attended attempts to produce specific changes on the chorio-allantoic membrane of the developing chick embryo. Andersen[13] believes that they have transferred the disease to pigs. In Denmark, porcine hepatitis is mainly caused by eating the tissues of pigs infected with porcine hepatitis. Findlay, Dunlop, and Brown[14] have made the suggestion that the disease might be due to a virus because of the length of the incubation period.

The exact incubation period is difficult to estimate as the period of infectiousness is uncertain. Cases reviewed in the Lapeer epidemic occurred in groups and seemingly were spaced at about an interval of one month. Most authors[1, 8, 14] have noted that cases occur either simultaneously or are spaced between twenty and forty days, usually twenty-one and thirty-five days. Glover and Wilson[8] thought there might be a form of the disease with an incubation period as short as four days. Most authors list their cases to show definite periodicity of the disease and assume that it is a contact disease with an incubation period of about thirty days. Blumer's review[3] of records from 1812 to 1923 stated that the incubation period usually is about seven to ten days and may be as short as two days and as long as twenty-eight days. These figures were said to have been obtained from the observation of the interval between primary and secondary cases in which the time of exposure with a secondary case was definitely fixed. Most English authors feel that the incubation period is at least one month. In two reviews, one by Cullihan[1] and another by Findlay, MacCallum, and Murgatroyd,[12] in 1939, it is stated that this is the probable incubation period. Molner and Meyer[9] make the statement that the largest number of cases had a probable incubation period of from two to three weeks. The only well-controlled evidence of the incubation period is the accidental development of jaundice following prophylactic immunization against measles. Thirty-seven children received 4.5 c.c. each of pooled convalescent serum and, after an interval varying between seventy-eight and eighty-three days, seven developed jaundice and became ill. Also in the report by Propert[15] in 1938 it was noted that two months after the onset

of jaundice in the seven children who had been immunized with convalescent measles serum, two other children in the same institution who had been in contact with the cases, but not inoculated with the serum, became ill with jaundice. Another suggestion as to the incubation period was noted in the report of hepatitis following yellow fever immunization described by Findlay and MacCallum.[16] In this it was shown that the serum in which the virus was grown was probably the etiologic agent for the hepatitis and that the interval between inoculation with the yellow fever vaccine and the development of hepatitis was from five weeks to seven and one-half months, with an average of from two to three months. There were apparently no symptoms during the incubation period. The period of infectiousness is probably short. Pickles,[5] in England, dating the disease from one possible exposure, felt that it was communicable in the preicteric stage. (In many epidemics it was thought to be four weeks.) Leucocyte changes are characteristically a leucopenia. An accidental infection of a laboratory worker as the result of working with sera from cases of infectious hepatitis is reported.[12] (Our medical technician developed a rather severe and protracted case of common infectious jaundice; she had handled numerous sera from these patients.) There is no laboratory animal which can be infected with infectious hepatitis. A comprehensive investigation has been made of hepatitis following yellow fever immunization.[17] Evidence was obtained to show that hepatitis was not due to yellow fever virus itself as the virus of yellow fever could not be isolated from patients with hepatitis at any stage of the disease. The hepatitis occurred in persons who were injected with yellow fever vaccine but who were already immune to yellow fever as the result of naturally acquired infection or as the result of previous inoculation. The extraneous agents introduced were chick embryos, distilled water, inorganic salts, and apparently normal serum. By a process of exclusion, it was thought that the apparently normal serum was the only possible vehicle by which this extraneous agent could have been introduced in the culture of yellow fever virus. The extraneous agent was presumed to be a virus because it was capable of being propagated in a serum-Tyrode medium containing chick embryo tissue, gave no visible growth on ordinary bacteriologic media, was not visible under the ordinary powers of a microscope, was freely filtrable through Seitz filters, withstood freezing and drying for many months when kept at 4° C., and gave rise to a disease characterized by an incubation period of from thirty-five days to seven and one-half months. This long and variable incubation period finds a parallel in certain other virus infections, such as rabies.

Propert[15] gave confirmatory evidence that a hepatotoxic agent, probably a virus, may be present in human sera. From eighty-two to 109 children in one block of a large institution for mental defects were inoculated with convalescent measles serum to protect them from the disease with which they had been recently in contact. After an interval

of from seventy-eight to eighty-three days these children developed jaundice and became gravely ill. No other child in the institution at that time had jaundice. An autopsy of the liver showed acute necrosis. Examination of the urine and post-mortem material for the Leptospira of Weil's disease was negative. MacNalty,[18] in 1938, in recording this occurrence of jaundice, stated that of the eighty-two to 109 persons who were inoculated with the same pool of measles immune serum, thirty-seven developed jaundice and seven died. Two other children, two months after the onset of the jaundice in the seven children who had been immunized with convalescent measles serum, developed or became ill with jaundice. Their illness did not appear to differ in any respect from true infective hepatitis. The distribution of the infecting agent is not known, but recently most authors feel that the virus gains access to the blood and is probably a hepatotropic virus causing acute or subacute necrosis of the liver.

Blumer,[3] in his report on infectious jaundice, says the leucocyte count varies. There may be a leucopenia or leucocytosis. More recently most authors, especially the English reviewers of this disease, state that there is no leucocytosis and often a leucopenia. They also state that there is a relative or absolute increase in lymphocytes or monocytes or both. Blood cultures have been consistently negative in all reported cases. Feces from sixty patients in the epidemic in Detroit reported by Molner and Meyer[9] were selected during the first week of the disease and bacteriologic examinations on these were negative.

Two forms of infectious jaundice are seen in the United States: Weil's disease and common infectious jaundice. Clinically this epidemic of jaundice did not resemble Weil's disease. It was mild with no complications or sequelae. The first differentiation between common infectious jaundice and the more serious Weil's disease, described by Felix Weil in 1886, was made by Cockayne[4] on clinical grounds. Later, in 1915, Inado and Ido[19] showed that the serious form of jaundice, or Weil's disease, was due to a spirochete later termed *Leptospira icterohaemorrhagiae* by Noguchi.

Usually the differentiation between an outbreak of epidemic jaundice and Weil's disease is founded on clinical and epidemiologic grounds alone, but in particularly severe cases a laboratory diagnosis is desirable. Weil's disease is recognized either by the demonstration of the Leptospira in the blood or urine or by guinea pig inoculation or later in the disease by the presence of specific antibodies in the blood serum. These are shown by agglutination or complement fixation tests.[20] The infection is transmitted to men from rats which harbor the Leptospira without developing the disease, the organisms being excreted in the urine. The disease occurs most commonly in miners, sewer workers, butchers, and others whose occupations expose them to skin contact with moisture or moist soil contaminated by the urine of infected rats. Individual cases

of Weil's disease have occurred during the course of an epidemic of infectious jaundice as in the Detroit epidemic.[9]

The exact definition of the type of jaundice is sometimes obscure. At one time all were described as acute catarrhal jaundice influenced by Stokes[21] and Virchow's[22] description of a catarrhal swelling of the duodenum and common duct with plugging of the lumen of the common duct. Later Heitler and Eppinger challenged this view and described a condition of infectious hepatic jaundice with "mild primary hepatic necrosis." These authors claimed that all infectious jaundice was primarily of this type. Later they admitted that apparently both types occur. Barber and Osborn[23] came to the conclusion that the majority of cases of benign jaundice are the result of a true hepatitis. They believe that hepatitis cases (infectious hepatic jaundice), both epidemic and sporadic, are due to some unknown agent which infects the liver. The duodenitis may be secondary and due to stasis.

The diagnosis of this disease, of course, depends upon differentiating it from the other types of jaundice. The only other type of infectious jaundice is Weil's disease. This disease is characteristically mild, but in any epidemic of jaundice Weil's disease should be ruled out by laboratory tests. Weil's disease is recognized either by the demonstration of the Leptospira in the blood or urine or by guinea pig inoculation, or later in the disease by the presence of specific antibodies in the blood serum. These are shown by agglutination or complement fixation test. The other differentiation is between so-called catarrhal type of jaundice and common infectious jaundice. There is no absolute method of differentiation between biliary obstruction and primary liver cell damage. These patients characteristically have a yellow type of jaundice and have no acute colicky pains. Examination of the urine usually shows urobilinogen or urobilin which would indicate that the bile ducts were patent and liver damage had occurred. This is an early sign of hepatic damage as it is said to be the first function to fail in a diseased liver.[24] Bilirubin is absent from the urine in infectious jaundice. These patients showed an elevated icterus index. Their van den Bergh reaction was either biphasic or delayed direct van den Bergh. Indirect reaction was moderately increased. Tests for hemolysis on the red blood cells of these patients failed to show any increased fragility. With biliary drainage on some of these patients at the height of their jaundice, bile was recovered. The galactose tolerance test showed impaired liver function. With the infectious nature of the disease, the failure to demonstrate *L. icterohaemorrhagiae* in the urine, the characteristic mildness of the disease, the presence of urobilin in the urine, and the impaired galactose tolerance test in all these reported jaundiced cases, it was considered to be common infectious jaundice due to a hepatitis.

Itching may occur but quite frequently does not. This itching is probably due to the presence of large amounts of bile salts in the blood

stream, and this probably does not occur very often in common infectious jaundice because jaundice rarely becomes that intense. The van den Bergh test is often a delayed direct or biphasic reaction. Comroe[24] comments on the color of the jaundice. Jaundice of primary hepatic injury is often orange-yellow, while obstructive jaundice is usually greenish.

There have been no reports of liver function tests on patients suffering from this disease, except in one epidemic reported by Yenikomshian and Dennis[11] in the Lebanese Republic, but this was done on a patient who later was proved to have pernicious anemia. They associated the onset of pernicious anemia with the common infectious jaundice, but it seems possible that they were dealing with a patient with pernicious anemia who showed jaundice. Comroe[24] states in review of toxic and infectious jaundice that a galactose liver function test done at the height of jaundice will usually show a decreased tolerance. Galactose is converted with difficulty into glycogen by the normal liver. A decrease in tolerance is associated with hepatic damage. Biliary drainage has been reported as a therapeutic measure, but there have been no detailed studies or reports of any studies on the results of biliary drainage either as to physical characteristics or as the result of culturing. Fragility tests have not routinely been done on any of the patients reported in the epidemics of jaundice except in a report by Schwartzman and Massey,[25] in which it is reported that fragility tests show no increase in the fragility over normal.

There has been noted a relationship of common infectious jaundice to acute and subacute necrosis of the liver. The clinical pictures are markedly similar apart from the greater severity of acute yellow atrophy compared to that of common jaundice. Cullinan[1] suggests that subacute necrosis of the liver unassociated with any known drug or toxin is seen quite frequently. Bergstrand[26] reported an average of two cases of acute yellow atrophy a year between the years 1914 and 1925. In 1925 and 1926 epidemic jaundice was prevalent throughout the country. In 1926 the incidence of acute yellow atrophy in Stockholm increased, and in 1927 there were forty-two cases. A pathologic picture of the cases reported in England of patients dying with common infectious jaundice was similar to that of those dying with acute yellow atrophy as reported by Bergstrand in Sweden.

As yet there is no specific treatment. Comroe[24] suggested that the treatment should consist of immediate removal of toxic substance if possible and the use of a diet high in carbohydrate, low in fat, containing approximately 14 per cent of proteins. It is possible to produce a high liver glycogen in dogs with common duct obstruction by large intravenous injections of glucose and high intake of carbohydrates orally. A greatly increased glycogen level does not protect the liver against injury if there is a high level of fat present. The protective role

of carbohydrate probably depends upon its displacement of the liver fat during the deposition of liver glycogen. It is also said by Comroe that an experimental toxic state can be produced in dogs with damaged livers by ingestion of meat; it has been suggested, therefore, that the proteins be in the form of milk, cheese, and egg white. Also, since the liver used glycine as a detoxicating agent, from 50 to 100 Gm. of gelatin may be added to the daily diet.

Schwartzman and Massey[25] state that in reviewing numerous reports no detailed dietetic studies were made, although the high carbohydrate, low fat diet is the one favored by many. In reporting their observations on the effect of diet, their impression was that regardless of the diet used the results were practically identical. They also stated that none of the diets caused any relapse of the gastrointestinal symptoms nor any exacerbation. Most authors have felt that these patients were not particularly sick and rarely required sedation or analgesics. They are usually more comfortable if they are kept in bed for a week or ten days after the onset of symptoms and then allowed up for a three-week convalescent period. This was especially true in adults but did not particularly apply to children.

Prognosis of the disease as to life is extremely good with but one exception in the epidemics reviewed. In the Hamet outbreak reported by Yenikomshian and Dennis,[11] only 6 per cent of the total number with the disease were children below the age of 10 years, while 25 per cent were adult females, with 68 per cent adult males. In elderly men the course was long with serious sequelae, two cases of subacute yellow atrophy of the liver being reported. In pregnant women the disease proved to be a more serious form, and in two cases it proved to be fatal. This is a decidedly unusual experience, and in most instances the only way autopsies are obtained in these patients are by accidental death. As to what the ultimate prognosis of these patients will be, no author has committed himself, and no study has been made, especially with regard to liver function.

SUMMARY

1. One hundred cases of common infectious jaundice have been observed in an institution for the feeble-minded.

A. Seasonal peaks for this epidemic occurred in the fall and winter.

B. Preponderant age groups affected were from 10 to 24 years.

C. Patients with low imbecile and idiot intelligence were most affected.

D. Incidence of jaundice in the static population as compared to the active population showed a ratio of five to one.

E. Liver function (galactose tolerance test) was regularly impaired during illness and was still impaired one year after illness in four cases.

F. Cultures of stools were negative except for *Staph. aureus.*

G. Biliary drainage was negative except for cultures of *Staph. aureus*, which probably represented contamination.

2. Conclusion drawn from comparison of facts in this epidemic with statements made in the literature are:

A. It is a contagious disease but does not seem necessarily conveyed by droplet infection.

B. The incubation period is probably one month.

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Critical Review

RECENT ADVANCES IN SCHOOL HEALTH SERVICE

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STUDIES and reports in recent years indicate a significant quickening of interest by pediatricians, as well as by public health and educational authorities, in this important, but relatively uncultivated, area of child health. The purpose of this review, which looks back about three years, is to familiarize pediatricians with developments which may have special importance for the future of school health service. An inventory at this time may have special value. After World War I, because of the revelations of the draft medical examinations, a great wave of legislation—introducing school medical examinations—swept the country. Before new statutes, stemming from the present conflict, are created, stock-taking would seem worth while.

The most promising development in the past three years is the growth of cooperation between departments of education, health departments, and other community agencies concerned with the health of the school child. This new spirit is a practical answer to that provocative question, Who shall administer the service? As states have created laws to protect the health of the school child until all states now have some legislation with respect to this, the dilemma has been intensified because in some instances the laws are imposed upon local boards of education, while in other instances the administration of the law is vested in state and local boards of health.[1]

GROWTH OF COOPERATION BETWEEN EDUCATION AND HEALTH AGENCIES

Groups of educational, medical, and public health authorities have actively studied this problem and have published their suggestions for its solution. Among the first of such reports was "Suggested School Health Policies."[2] This outlined the responsibilities of schools and related the school health program to the health programs and activities of other community agencies. It emphasized that school health programs develop best in an atmosphere of full cooperation between education and health groups. The report itself represented an achievement in cooperation between organizations. Eight national groups or committees gave the report their serious attention and support. The School Health Committee of the American Academy of Pediatrics[3] recognized this development when, in 1941, in summarizing progress in school health, the comment was made that "[School health] policies are

being defined with long-range planning by educational, public health, and medical leadership, and in some places there is evidence that mutual appreciation of the others' problems and clear definition of what each shall contribute to their solution is replacing mere school or health authority." In the 1942 Yearbook of School Administrators, "Health in Schools,"[4] it is pointed out that "responsibility rests upon the school superintendent and the local health officer for working together to establish an effective relationship between the health program of the schools and that of the community, and for bringing other agencies to their council table to plan, jointly, a community program of health education." A concrete illustration of the successful application of this policy was contained in a bulletin published by the Michigan State Superintendent of Schools, "The Health Services in the Schools."[5] Not only are policies for environmental sanitation, health of school personnel, appraising the health of the school child, and other aspects of school health service recommended, but also are emphasized the educational implications of these policies. The "Astoria School Health Study" was a convincing demonstration of what may be achieved by "men of good will" working together.[6] This study was brought about because the administrators of the New York City Departments of Health and Education, who have a joint responsibility for the health program, wished to find more effective ways of conducting the service.

Among organized medical groups, the Medical Society of the State of New York, through its Council Committee on Public Health and Education, has been interested in the school health program for several years.[7-10] Close working relationships have been established with the State Departments of Education and Health, the New York State Association of School Principals, and the Dental Society of the State of New York. The Medical Society has concerned itself with the following phases of the school health service:

(a) Administration of the service at the state level

(b) Standardization of the physical examination for school children and other youth groups

(c) Health education in the elementary and secondary schools, including a required formal course with credit in high school

(d) Course content for health instruction in the high school

(e) Qualifications for school physicians serving less than half time

(f) Undergraduate instruction of medical students in school health

(g) Postgraduate instruction in school health

(h) School health committees for county medical societies (forty-four of the sixty-one county medical societies now have committees on School Health)

(i) Rheumatic fever and rheumatic heart diseases as a part of the school health program

(j) Health examinations, including x-rays for teachers and other personnel as a part of the tuberculosis control program (this has been receiving attention during the present year, especially by the Subcommittee on Tuberculosis and Diseases of the Chest)

Two important products emerge from this cross-fertilization of the disciplines of education and health: (a) increased understanding of the educational values in school health service; and (b) recognition of the relationship between school health service and the public health program of the community. This cross-fertilization, if fostered, will create a school health service better adapted to modern education and public health practice.

PREPARATION OF HEALTH PERSONNEL

Second only in importance to the growth of interagency cooperation is the attention now being directed to the preparation of health workers in the school health program. The training of physicians for school health work has been outlined by Kleinschmidt[11] and also by Senn.[12] The School Health Committee of the American Academy of Pediatrics[13] has recommended standard qualifications for school physicians and suggested medical advisory committees as aids in the administration of school health service. The Board of Education of Pelham, N. Y., recently announced that it was using these recommended standards of the American Academy of Pediatrics as a guide in the selection of its new school physician.[14] The Committee on Professional Education of the American Public Health Association is preparing a report on the educational qualifications of school physicians.[15] All of these statements stress the importance of experience and training in the fields of pediatrics and education.

In many schools today the school nurse is the only health specialist. There has been a remarkable growth in the number of nurses employed for school health. In 1938 a census of public health nursing revealed that approximately 17,000 nurses were employed either full or part time to render health service to schools.[16a, 16b] The National Organization for Public Health Nursing has suggested minimum qualifications for nurses appointed to school positions.[17] Sixteen state boards of education have established state certification requirements for school nurses.[18] The roles and the qualifications of dentists, oral hygienists, psychiatrists, psychologists, and nutritionists in the school health service have been discussed.[18] Kleinschmidt[19] has reported on the educational opportunities for teachers in health education. While World War II has aggravated the shortage of health personnel in the schools, this attention to the development of standard qualifications for health specialists is laying a firm and broad foundation for the school medical service of the future.

THE EVOLUTION OF THE SCHOOL MEDICAL EXAMINATION

The school health examination has long been accepted as a primary function of school health service. The medical findings among American draftees examined during World War I were a powerful influence in securing the enactment of laws regarding medical inspection of school children. In the period 1917-1924, such laws were passed in twenty-four states. Now, forty-three states have a statute either permitting or requiring the examination of children for physical (and sometimes mental) defects.[1] The school medical examination as performed annually or "routinely" has been severely criticized both as a costly and inaccurate case-finding method[20] and as a bad educational experience.[21] As educators and pediatricians realize that medical procedures in the school can and do have educational implications, the trend is toward fewer, but more thorough, medical examinations for individual pupils. The value of the presence of the parent at the examination, especially of younger children, in terms of health education as well as treatment, was demonstrated by Walker and Randolph[22] and by Nyswander.[6] In the elementary school, according to Wheatley, the school examination resembles a health conference. The school physician, in appraising the health status of the child, utilizes information based not only on the physical examination but also on the interview with the parent and, frequently, with the school nurse, teachers, and other members of the school staff.[23] Wilson[24] called attention to the educational opportunities of the school examination. Spock[25] has demonstrated how the modern school physician contributes to the guidance program of modern education. The American Academy of Pediatrics[3] reported that in many communities the functions of the school physician and nurse are being defined in terms of health education.

As the school medical examination has become an improved instrument of health education, it has become more time consuming and consequently more costly in case-finding. Efforts have been made to develop more practical means of health supervision and case-finding among school children. These have been: (a) use of screening procedures annually or semiannually to detect children with poor vision and hearing and other specific abnormalities; (b) promotion of teacher interest and observation of pupil health from day to day; and (c) stimulation of the participation of the private physician and dentist in the school health service.

EXPERIENCE WITH SCREENING TESTS

The Snellen test for vision defects is the best known of screening tests in the schools. The Division of Child Hygiene of the Massachusetts Department of Public Health studied the Snellen test as usually given in the Massachusetts schools and concluded that the test is too coarse a screen.[26] The outcome of this survey is a new method of testing the vision of Massachusetts children.[27] On the other hand, the Astoria

Study demonstrated that the Snellen test, when used in combination with teacher observation of signs and symptoms of eye strain, is a practical method of screening vision defects.[6] As in the Massachusetts study, the Astoria report emphasized the necessity of maintaining standard testing conditions. The Astoria Study also showed teachers may be as accurate as nurses in the selection of visual defects. It was recommended on borderline cases of 20-30 and 20-40 that the nurse check the teacher's score, but on severe defects of 20-50, or worse, it was unnecessary to have the nurse retest the children.

Audiometers are gaining in popularity as a screening device for defective hearing. There is a difference of opinion as to whether it is necessary to employ the group test and the individual test for school purposes. Wells[28] has recently described its use as a part of an aural program appropriate for a large English city. With some modification for local custom, the plan is suitable for American communities. The initial step is to test forty children at one time. Those who fail are given a second test and, if under 11 years of age, are given a third test, preferably on the same day as the original test. They are examined by an ear, nose, and throat specialist to determine the reason for failure. The experience of the Astoria study revealed that individual testing by the audiometer was unnecessary if the group test is done carefully and failures are checked by repeat tests.[6] Some appreciation of the frequency of impaired hearing among school children is revealed by a hearing survey among 32,269 white children in the second, fifth, and eighth grades in Maryland schools by Bjorlee.[29] It was found that 87.4 per cent of the children had normal hearing, 10.3 per cent had a hearing loss of less than 15 per cent, and 2.3 per cent registered a hearing loss of 15 per cent or more. With respect to prevention, Crowe[30] has found that radon irradiation of the nasopharynx will improve the hearing in selected cases. Crowe says that "a large number of cases of handicapping degrees of deafness could be prevented annually by prompt medical care of all new cases of acute otitis media." Use of the otoscope in school medical inspection would probably detect many such cases. Wilkins[31] has shown that the otoscope in routine medical inspection detects a larger number of important defects than does the stethoscope and may therefore be considered of greater value as a diagnostic instrument in the hands of the school physician.

A more recent screening device which has been offered to school health service is the Wetzel Grid,[32] which utilizes height and weight to evaluate growth and development. The author assumes that (1) there are seven general types of physique among children of elementary school age; (2) the normal tendency is for children to adhere to their "type" throughout their period of growth and development. He has developed an ingenious chart divided into seven channels to correspond to the seven body types. When height and weight are plotted on this chart, he found that normal children will stay in their "channel."

Deviations from the channel call for medical investigation of the child. The author describes the application of the Grid to the health supervision of school children. Bruch[33] has studied the usefulness of the Grid in evaluating basal metabolism and bone development in fifty-two children with abnormal bodily dimensions. She found that the relative advancement or retardation of statural growth (height-age) could be judged from the Grid but that the Grid's interpretation of "developmental age" did not agree with the individual's developmental age as determined by x-ray of the bones, nor did its interpretation of basal metabolism, as determined by laboratory methods. She did think the Grid would be useful in screening out children with abnormal body proportions and disturbances in developmental progress.

It is important to recognize that these screening devices do not replace medical judgment. They merely select children who do not perform the test satisfactorily. In the case of those who fail to pass the vision and audiometer tests, special examination by ophthalmologists and otologists is necessary to determine the reason for failure.

Some school health services have applied the screening principle to other phases of the health examination. Heart disease is a relatively common and serious finding in children of school age. The usual periodic school examinations are very unsatisfactory for the accurate diagnosis of heart disease. Some communities do not permit the removal of clothing; the school physician has only a few minutes to spend on individual children; he does not have the advantage of a fluoroscope or x-ray. In New York,[6] Cincinnati,[34] and Rochester, N. Y.,[35] the school physician "screens" out possible cases of heart disease. These children are referred to a diagnostic service where the examining specialist has the advantage of more time and laboratory aids for a diagnosis. By this careful procedure more accurate diagnosis of a serious condition is assured and modification of the school program can be based on a clearer understanding of the child's physical potentialities.

THE CLASSROOM TEACHER'S ROLE IN HEALTH SERVICE

Nyswander[6] demonstrated that the teacher's responsibility for observing the health of her pupils can be made an effective part of the school health service. Teachers were prepared to observe and report to school nurses the health condition of pupils. The annual school medical inspection was replaced by annual and semiannual conferences between classroom teacher and school nurse. After teachers had received preparation, eight out of every ten children selected in these conferences, when examined subsequently by the school physician, were found to have a health condition requiring further medical attention. The study also revealed that teachers need more knowledge of and experience in observing health behavior and recognizing health deviations. It should be understood that this preparation of teachers is not for the purpose of assuming work to save the time of nurses and physicians but

primarily to enable the teacher to perform more ably one of her important responsibilities. The State Superintendent of Schools in Michigan has published a helpful guide to aid teachers in the observation of the health of pupils.[36]

INTEGRATION WITH COMMUNITY HEALTH SERVICES

It is more widely appreciated now that the community medical and dental facilities are essential parts of health service for the school child. Evidence of the private physician's increased participation is offered by Kantrow,[37] who reported that in New York City, as a result of the parent-education program by the Departments of Health and Education, the proportion of health examinations made by private physicians over a period of four and one-half years rose from 14 (18,022) to 36 (33,954) per cent. Lifson,[38] Turner and associates,[39] Morris,[40] and Kramer[41] have each described successful plans of cooperation with community dentists to secure service for school children. The trend is to give more thorough medical examinations to new pupils and, perhaps, to repeat examinations at stated intervals during the rest of the child's school career and to use screening devices to select possible defects of vision and hearing because these tests are sufficiently precise and comparatively economical procedures. The services of the school physician are preserved to evaluate and interpret the results of these tests and the reports of family physicians and other community treatment agencies to the school authorities.

RECENT ENVIRONMENTAL STUDIES

Heating, lighting, and ventilation are the environmental factors which have been intensively studied in the past. More recently, experimentation in environmental control of contagion has been reported. Wells, Wells and Wilder [42] described the control of communicable disease by ultraviolet radiation of the classroom atmosphere. This method, as well as the use of aerosols reported by Robertson,[43] has potential application in classrooms, not necessarily to postpone childhood contagious diseases to older ages, but rather to prevent the occurrence of communicable diseases at unfavorable times, such as measles in mid-winter when the danger of a complicating streptococcal infection is highest.

As knowledge accumulates regarding the streptococcus, more precise methods of managing outbreaks of scarlet fever and other infections due to the streptococcus may develop. Boisvert and Bearg[44] have suggested a future pattern in their study of an epidemic of scarlet fever in a kindergarten in New Haven in 1940-1941. By isolating the type of streptococcus which caused the outbreak, it was possible to identify those children in the group carrying the streptococcus capable of producing the disease. Schwentker[45] controlled an outbreak of scarlet fever by administration of one of the sulfonamides.

Wheatley[46] has called attention to the fact that school communicable disease procedures have not kept pace with present-day knowledge of the epidemiology of these diseases. Periods of quarantine and isolation are too long for many of the diseases. He suggested that review of local communicable disease regulations by the health officer and school administrator is a timely subject for cooperation, especially in localities where state aid is related to school attendance.

An elaborate program of environmental control is reported by Harmon of the Texas State Department of Health. His investigations[47] suggest that environmental conditions in the classroom may be factors in the development of health problems. Among the findings he reports are: (a) 49 per cent of children with eye defects had already developed body asymmetry or were subjected to poor environmental conditions, such as improper lighting and seating, which might tend to produce body asymmetry; (b) about two-thirds of the children with nutritional deficiencies were in classroom situations where programs were not related to their physiologic needs or their natural physical capacities; (c) behavior difficulties increased from 4 per cent to 10 per cent during elementary years.

Attention is centered on the school lunch as a factor of increasing importance in the school child's environment. Koehne[48] suggests ways of developing a strong school lunch project which makes the lunchroom and the noon meal an integral and vital part of the health education program of the school. Mention is also made of undesirable dietary practices followed in many schools, such as the sale of candy, commercial fruit beverages and soft drinks, potato chips, and popcorn, which divert the child's lunch money from the purchase of needed nourishment.

It is impossible, while interpreting developments in school health service, to ignore the influence that the mental hygiene movement in recent years has had on such service. In addition to the abundant literature relating to mental hygiene in the classroom, there is evidence that the school medical service has recognized the importance that emotional disturbances, especially in wartime, can have on the health of the school child. Patry[49] suggested that school physicians and nurses take cognizance of significant change in the child's habitual reactions. Abnormal forms of fear, anxiety, hate, aggression, tension, insecurity, confusion, excitement, depression of spirits, and unhappiness are all symptoms which must be evaluated. Spock[25] said a large number of cases of poor appetites, poor sleep, overactivity, and poor school work are directly ascribable to inner emotional disturbance, often traceable back as far as infancy. If the school physician is to learn about these children and interpret them to the school, he must get as much history as possible and get it from a psychosomatic point of view.

Recently special classes for physically handicapped children have received serious evaluation by committees of educators and physicians

appointed by the New York City Board of Education.[50] In general, among the medical findings it was agreed that the physical condition of many of the children then in special classes was such that they could attend regular classes with either a full or modified program. Further, that "special programs show little evidence of recognition of the differences in children's needs, abilities, and interests nor the necessity for directing them toward ultimate adult adjustments compatible with their limited capacities." The Committee concluded that there were neither medical nor educational reasons for the existence of open-air classes. They made many recommendations intending to improve the operation of other special classes for physically handicapped children.

WAR'S IMPACT ON SCHOOL HEALTH SERVICE

The war has brought new problems to the health services in the schools. On the one hand, there is an increasing shortage of physicians and nurses—never an oversupply in this field. On the other hand, the schools are being called on to extend their services to fill the gap in the daily lives of children because of the disorganization of family life resulting from many parents' going into military service or industry. The necessities of war have made administrators of school health service study the functions and methods to determine what practices are most essential and what functions may be safely discarded or assigned to less highly trained workers. Swanson,[51] Grout,[52] McNeil,[53] and Ross[54] have discussed the school nurse's task and suggested ways of conserving the school nurse's time. Willard,[55] in outlining a constructive program of school medical service for wartime conditions, urges that more attention be given to the development of adequate treatment facilities. The Joint Committee on Lay Participation in School Nursing[56] has made a statement of policy to guide school administrators in effective use of the school nurse during wartime.

The extension of the school program not only to care for children of school age but to include children of preschool age is adding new responsibilities to the school health service. There are advantages to this situation because these new problems are a challenge. From the preventive point of view more constructive health work can and should be done with the preschool group. Many of the dental and medical findings and behavior disorders observed among kindergarten and first-grade children have begun at ages 3 and 4. The Victory Corps program and the increase in vocational high school enrollment have made great demands on the school health service in many communities. The medical examinations of this older age group reveal many neglected health conditions and reflect the inadequacy of health programs in most high schools and vocational training schools. Schmidt[57] recently reported on a study of health conditions among high school students on the Lower East Side of New York and proposed a health service to meet their needs. The University High School health program

in Oakland, Calif., has features which other schools might study and follow.[58] This broadening of the age group served by the school health service has the further advantage of further integrating the school health work with the community health program.

CONCLUSION

Within the limits of this review it has been possible to sketch only some of the high lights of more significant developments in school health service. Some gaps are inevitable. Specific research in growth and development of great significance in school health service has been omitted. Very little was said about dental service, which is an integral part of the school health and public health service. To describe the research on health conditions found in children of school age, as, for example, skin conditions, tonsils, heart disease, nutritional and emotional disturbances, would require a separate report of pediatric literature. Attention was given mainly to interpretation of trends affecting the administration of school health service. These are: (a) developments which indicated better understanding between departments of education and health in carrying out school health service; (b) administrative procedures based on several recent important studies which bring school health service more into line with modern pediatric, educational, and public health practice.

There are still great distances to travel. We must not permit the war to close our minds to further progress. In fact, the emergency can be used to discard inefficient, outdated practices. A more critical view of school medical work is needed. "We need the courage," Willard[55] has said, "to cut our programs to fit the pattern revealed as valuable by rigid objective studies, even though such cutting treads upon the sanctified toes of tradition." With "business as usual" discarded for the duration, the present is a rare opportunity to experiment and build for tomorrow. As Raymond Fosdick has stated, "We must make the present serve the future."

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News and Notes

The following are members of the Special Committee for Cooperating With the Children's Bureau With Regard to the KMIC Program:

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Dr. Raymond W. Hold, of Niagara Falls, N. Y., died recently from carcinoma.

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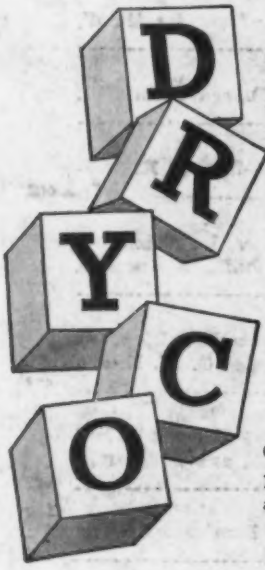

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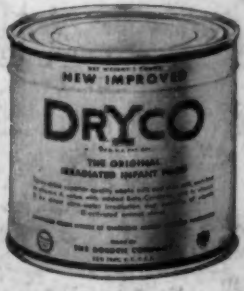

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